

Proceedings of the Sixth International Tinnitus Seminar

Edited by Jonathan Hazell FRCS

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The use of science to find successful tinnitus treatments

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Discovering successful treatments will be facilitated by the scientific method. Patient expectations dramatically influence treatment outcomes, and therefore require careful consideration in selecting control conditions. The population under study requires careful definition of recruitment and exclusion practice, duration and severity of tinnitus, hyperacusis and hearing loss. It is also desirable to document ear disease, psychological and psychoacoustical characteristics, treatment history, otoacoustic emissions, whether tactile or motor stimulation effects tinnitus, and whether the tinnitus is likely consistent with a peripheral or central mechanism. The most challenging aspect is designing the appropriate control condition. A comprehensive description of the protocol is needed to facilitate replication. Benefit should be measured with established questionnaires and with measures of the magnitude of the tinnitus. A persuasive tinnitus treatment will be one that shows a large treatment effect, can be generalized across patients and clinicians, is specific and credible, and changes the way we think about tinnitus.

Introduction

As we begin this conference, let me state that I believe there are no widely-accepted treatments that have been shown to be effective for tinnitus. In this article I hope to provide a framework for clinical trials for tinnitus treatment. Good research is the best avenue to good treatment.

The scientific method

The scientific method is a tool for uncovering truth. Through clearly defined methods and reasonable data analysis, the effectiveness of different treatments can be evaluated. In the reality of clinical trials, some compromises are often required. But if the essence of the scientific method is compromised, it may render the experiment difficult or impossible to interpret. An inadequate study may be misleading, and is often worse than no study at all.

For me, I have always perceived that the heart of the scientific method is that the protocol be clearly defined so that it can be replicated by others. New treatments need to be described in writing so others can evaluate their effectiveness. Treatments need to be replicated by independent investigators who have no ties to the initial work.

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Patient expectations

As a preamble to discussing scientific methodology and tinnitus, it is particularly important to highlight factors that indirectly contribute to successful tinnitus treatment. Understanding the patient-clinician role is critical to designing adequate clinical trials and interpreting results.

Brown [1] has summarized some interactions between patient and therapist that should be read by everyone involved in tinnitus care and research. He describes a situation in which he called his cousin, a physical therapist, for assistance with back pain. His cousin had provided useful help in the past. His cousin recommended that he should place an ice pack on the area, prescribed some specific stretching exercises and suggested that he take ibuprofen. Brown reported that immediately he felt better, even if his back was not better yet. However, he later pondered whether it was the treatment that was helpful, or whether it was the act of seeking and receiving treatment. If you leave the office feeling like you have seen a sympathetic, caring specialist who understands your illness and who has provided you with a clear therapy plan, you are often on the road to recovery.

The helpful 'placebo' factors that Brown and others have identified include the following: Seeing a professional, receiving a plausible treatment plan, and believing that the treatment will work.

This placebo effect is often thought of as evidence of patient susceptibility to non-treatment factors,

but in fact a closer look indicates that some patients do improve their health under such conditions. Let me repeat this: "If the patient believes that are going to be helped by a treatment, even a sugar pill, then they often receive a real, beneficial effect". In fact, this effect is sometimes accompanied by physiological changes [2].

Brown [1] proposed that health care workers make better use of this placebo effect, and actually incorporate its healing effects into their practice. I believe that such an affect has an enormous impact on the treatment of tinnitus patients and should always be accounted for in designing treatment experiments. I prefer to call this effect Patient Expectation Nurturing.

Influencing patient expectations

There are several things that we can do to influence a tinnitus patient's expectations, and promote a feeling of control and hope.

Being perceived as a knowledgeable professional

The clinician should be seen as appropriately and well educated, be dressed formally, have an elegant office, act responsible and be respectable. Factors that contribute to being perceived as being well educated might include a professional title (for example, being called doctor, wearing a white 'lab' coat or a suit, and having educational certificates on the wall). These attributes, of course, do not guarantee the perception of an esteemed professional, and may also have negative consequences if carried to the extreme or if perceived as pompous. Nonetheless, through dress, attitude and environment, it is important that the patient perceive you as being a knowledgeable professional.

Be sympathetic towards the individual

Many patients are very distressed by their tinnitus. They need time to share their problems. They need someone who will be a good listener. The clinician should be sympathetic and can share similar stories from other patients. They need to know that you appreciate that they have a serious problem, and that you understand that it can create many hardships.

Demonstrate that you understand tinnitus

It is important that the patient believes you are knowledgeable about tinnitus. Most patients have gone from one professional to another and have received brief, tentative counseling. They get the feeling they are being "brushed off", and that nobody really understands tinnitus. You can demonstrate your knowledge about tinnitus very simply. Discuss the causes, the prevalence, the typical symptoms, provide reassurance and review the treatment options. In some cases the mechanisms can also be

described depending on the sophistication and interest of the patient. A hearing aid is often helpful. This information will not only demonstrate to the patient that you understand tinnitus, but will also provide useful knowledge to the patient to take the mystique out of tinnitus.

Provide a clear therapy plan

If patients believe there is an efficient strategy, they no longer feel helpless. Patients benefit from being involved actively in their treatment. It engages them in a way that they feel like they can be part of the solution. The particular therapy may not be so important. Although some therapies might be better for some individuals, it is not always the specifics of the therapy plan that are important. What is critical is that there be a plan, that it is well defined, and the therapist and patient believe that it is reasonable and achievable.

There very well may be some therapy plans that have a stronger placebo effect than others. For example, it is not known whether frequent contacts, by phone or office visits, are desirable. Would it be useful for the patients to have something to do everyday? How long should this activity be? Should it be at the same time daily and should the patient keep a diary of these activities?

Show that you sincerely care

Another factor involves demonstrating to the patient that you sincerely care about their well being. This will be demonstrated in the time that you spend with them, the manner in which you listen and ask questions, and by showing that you want them to succeed.

Clear definition of population

Tinnitus patients differ widely and the success of any particular treatment will be influenced by many factors. I recommend two categories defining the population. The first category is 'essential characteristics', which I believe should be reported in every study. The second category is 'recommended characteristics', which I think are desirable.

Essential characteristics in defining the population

Recruitment criteria. It is important to know how patients were recruited for the study. Where did the patients come from? Were they an unselected sequential group of tinnitus patients? Were they self-selected and self-referred? This might suggest they are different from the tinnitus population at large. This information is critical to determine how the results generalize to the entire population of tinnitus patients. Tinnitus patients could be sequential patients who are seen at a clinic, they could be patients who are selected by the

experimenters as desirable in some (definable) way, or they could be patients who self-refer after hearing about the therapy on the internet or in the newspaper.

Exclusion criteria. Not every patient may be desirable as experimental subjects, and some subjects may drop out for various reasons. This is not necessarily a problem, though it influences the how the findings can be generalized. Were any patients excluded from the study? Were any patients excluded from the data analysis?

Severity of tinnitus. The effectiveness of any treatment might depend on the severity of the tinnitus. Less severe patients, for example, might be less motivated to follow a protocol. Alternatively, more severe patients with psychological disorders might be more difficult to treat. The severity of the tinnitus handicap can be defined with several established tinnitus handicap/disability scales [3,4, 5]. In the Kuk *et al.* scale [3] the patients score can be compared to the population at large (Figure 1). If the therapy aims to reduce the tinnitus, then the tinnitus itself should be measured with the loudness matching and broadband noise masking.

Hyperacusis. There appears to be a greater proportion of tinnitus patients with hyperacusis compared to patients with hearing loss without tinnitus [6]. Hyperacusis may be intimately related to the mechanism of tinnitus [7], or it could be unrelated to the mechanism but a manifestation of the same disease. Treatments that include sound stimulation should definitely report whether their patients have

hyperacusis. It is helpful to state how it was defined and how it was measured.

Figure 2 presents a schematic for defining terminology in this area. Hyperacusis represents an uncomfortable loudness level that is lower than normal. Standard instructions and data are available [8]. I recommend reporting the uncomfortable loudness levels at 500 and 2000 Hz, where most data are available from the hearing impaired population. Hypersensitivity is when hearing thresholds are better than normal. Phonophobia is a fear of sounds.

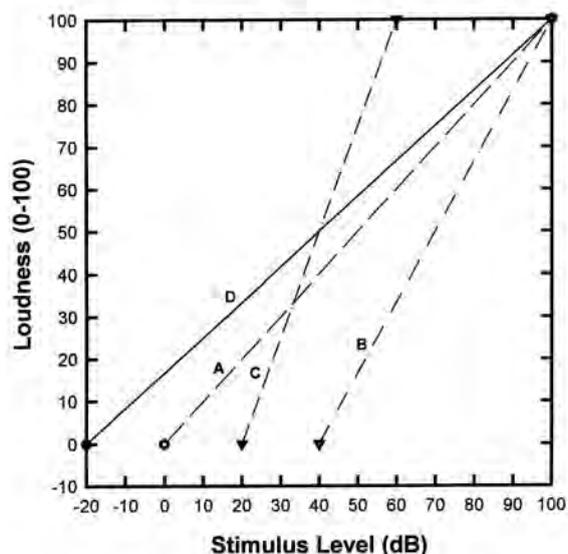


Figure 2 Perceived loudness in arbitrary units as a function of stimulus level. A = normal, B = recruitment, C = hyperacusis (over-recruitment), D = hypersensitivity.

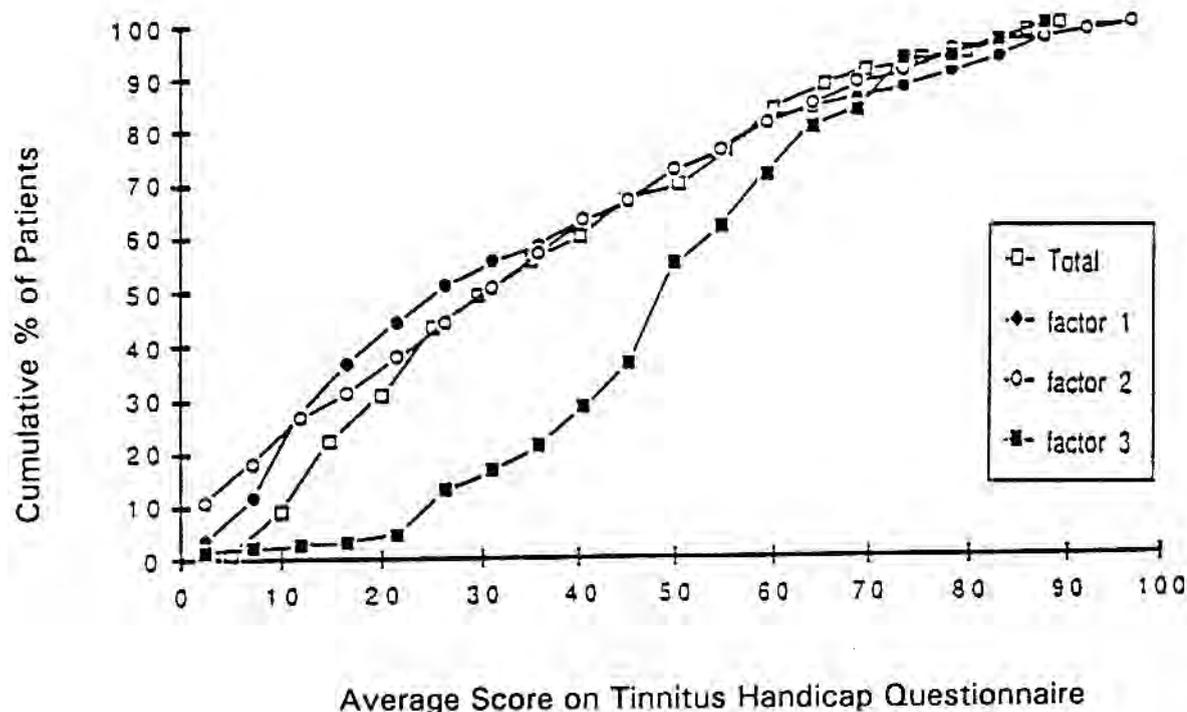


Figure 1 Cumulative distribution of scores on Tinnitus Handicap Scale from 275 patients [3]. An individual's mean score of 75, for example, is greater than 95% of clinic patients with tinnitus.

Duration of tinnitus. It might be that a long-duration tinnitus is more difficult to eradicate than a short-duration tinnitus. Or, that patients who have only experienced tinnitus for less than a year might be experiencing more psychological difficulties and therefore might be more difficult to treat. Knowing the duration of tinnitus could be helpful.

Severity of hearing loss. The severity of the hearing loss is one good indication of the extent of abnormal functioning in the cochlea. It is very rare to have no evidence of hearing dysfunction in a patient with tinnitus. I consider at 15 dB HL loss at 4000 Hz and 0 dB HL threshold elsewhere as evidence of hearing dysfunction. I recommend reporting (at least) the 500-Hz and 4000 Hz thresholds. Averaging across frequencies loses information.

Desirable characteristic to report

Psychological profile. Many patients have psychological entities that may effect treatment. It could be critical to know which patients are clinically abnormal verified by standard psychometric measures.

Ear disease. Did the patients have noise-induced hearing loss, Meniere's syndrome, presbycusis, or head injury?

Tinnitus treatment history. What other treatments has the patient experienced? How long were the trials? Were they helpful?

Description of tinnitus. Patients often describe their tinnitus in very different ways. This description is likely influenced by previous experience. Nonetheless, I believe it could be helpful to distinguish patients who report: a tonal versus diffuse tinnitus, a single sound versus multiple sounds, continuous versus intermittent tinnitus, and whether tinnitus is perceived as unilateral, bilateral or in the head.

Psychoacoustical profile of tinnitus. Several years of measuring tinnitus have resulted in some very different types of responses among patients. It could be useful to document: postmasking effects [e.g. 9], the pattern of tonal masking, the effectiveness of a masker over time [10], and pitch. In a controlled study Donaldson [11] noted that the pitch-match frequency decreased following amylobarbitone treatment.

Central versus peripheral. There is no certain test that differentiates between peripheral and central tinnitus. It may be that tinnitus which originates peripherally eventually has central components as well. Nonetheless, I believe there is merit in attempts to distinguish peripheral versus central tinnitus based on current understanding. It is more likely that tinnitus is central if:

- Tinnitus is perceived in the head,
- If the patient has a unilateral hearing loss and a bilateral tinnitus,

- If a unilateral masker reduces the tinnitus in both ears of a patient with bilateral tinnitus,
- If a contralateral masker is effective in reducing the tinnitus in a patient with unilateral tinnitus,
- If the tinnitus cannot be masked (see Figure 3),
- There is no frequency specificity to tonal masking of the tinnitus (see Figure 3) [12],
- An ipsilateral masker does not alter the perceived location of the tinnitus within the head.

Otoacoustic emissions. There are a small number of patients with tinnitus and an associated spontaneous otoacoustic emission. It would be useful to identify these individuals.

Influenced by tactile stimulation. Recent work and my own clinical experience has shown that some patients report a change in their tinnitus as a result of body movements or pressure on the skin, usually around the face and hands [13]. These patients might be different in some very important manner.

Allocation to treatment/control groups

The standard protocol in clinical trials is to have two groups, one receiving the treatment and one not. There are two ways to assign patients to these two groups; randomly and selectively matched. Dobie [14] provides an excellent review of this topic [see also 15].

Random assignment is desirable because there can be unknown variables which are not accounted for in the matching. However, the random assignment assumption of group similarity is true only when the groups are large. This is a valuable approach in tinnitus treatment research because no predictor variables for treatment success have been identified.

Matched clinical trials are desirable to ensure better equality among groups and when smaller groups are to be tested. However, there is usually difficulty in knowing all the important factors to match, and how closely to match. In tinnitus research, matching could involve ear disease, hyperacusis, and severity of tinnitus. If further matching were possible, virtually all the factors mentioned above under "definition of the population" could be included. This is also a desirable approach in tinnitus treatment research, because tinnitus is not the same in different patients, and a single treatment might not work for everyone.

Controls

I believe the most important ingredient in discovering factors that lead to successful tinnitus treatment is the use of adequate controls. In fact, I would suggest that we need more-than-adequate controls in tinnitus research.

These controls need to include all factors that encompass patient expectations. Therefore, a waiting-list control is clearly inadequate, as patients don't expect to get better as they are waiting for treatment. Placebo medications which have some

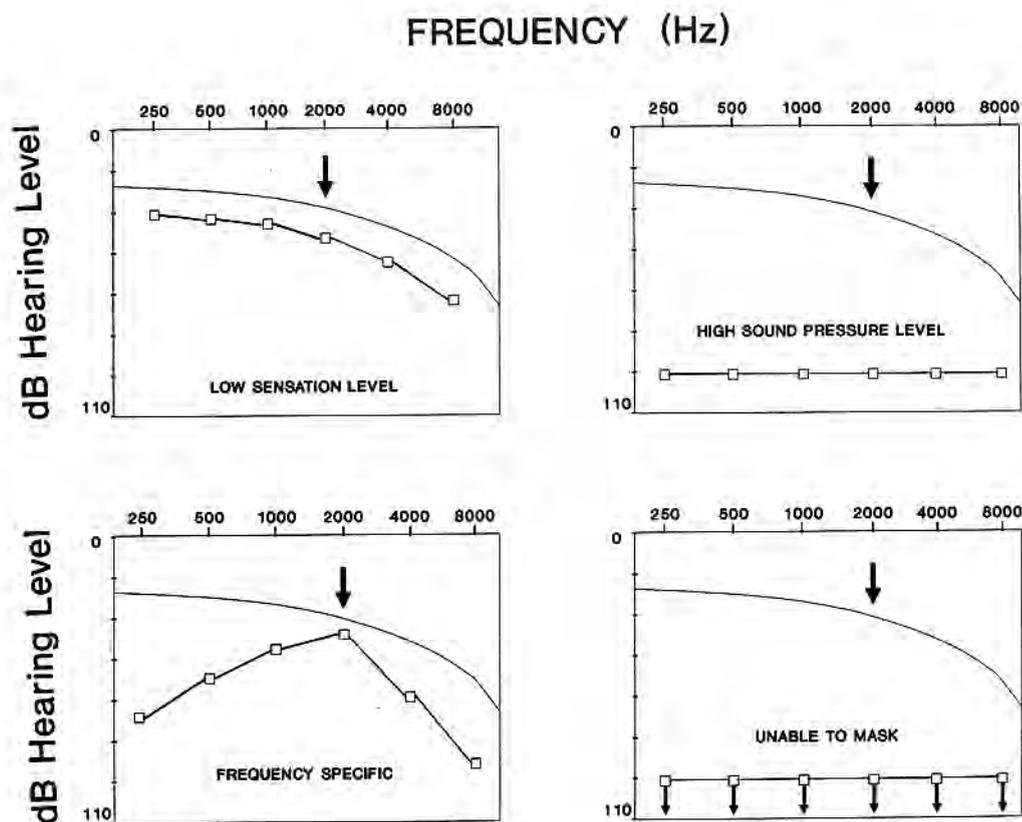


Figure 3 A schematic of different pure-tone masking patterns. Frequency specific masking suggests a peripheral tinnitus and a high-level pattern or unable to mask suggests a central tinnitus [12].

minor side effects would be desirable as they render it more difficult for the patient to guess the placebo. Using two experimental groups instead of a placebo will not help, as both 'treatments' could be influenced by the placebo effect [14].

Thus, the control and experimental condition must be matched on:

- Patients perception of credibility of therapist;
- Nurturing;
- Device counseling;
- Patients perception that the treatment will work;
- Directive counseling;
- Enthusiasm, experience, sympathy and confidence of therapist;
- Frequency and number of contact hours.

Blinding

Where possible, it is desirable to blind both the patient, and clinician data-gatherer to which is the experimental condition and which is the control conditional. In drug research, this is straightforward. In experiments using sound therapies, however, it is also possible. For example, the patient could be told there are two forms of this treatment that we are testing. Two different sounds can be used, and the patient doesn't know which one is the

treatment under test. The clinician who fits the sound therapy devices does not have to be the clinician who counsels and tests the patient. Therefore, at least part of the fitting and the testing can be blinded.

Clear description of treatment

I have already mentioned the importance of describing the therapy plan so that others may replicate the procedure. Someone who is trained as a psychologist, an audiologist or otologist should be able to read about the therapy and provide treatment. I suppose that some procedures could be so complicated and require special training that some kind of 'board certification' could be required. This approach is rare in health care professions. I am not aware of any tinnitus treatment that is so complicated that a written text would not suffice to describe the procedure. Maybe some test is required for competency in a procedure. The test must be based on data supported by facts.

Measurement of benefit

Tinnitus can be treated in two ways; we can decrease the magnitude of the tinnitus or the

patients' negative reaction to the tinnitus can decrease. The goal should be clear.

Tinnitus magnitude can be measured by measuring tinnitus loudness and by measuring the level of a broadband noise required to mask the tinnitus.

There are now several handicap measurement tools that are available with established and acceptable statistical properties [16]. I recommend using three in every clinical trial [3,4,5]. Clinical trials should not be based on 'home made' questions whose statistical properties have not been tested rigorously.

I also have patients rate their loudness and annoyance on a scale from 0 to 100. Patients usually select the 5-point increments, providing a 20-point scale. This allows more resolution than a 7-point scale. In my experience, patients are very comfortable using a decimal system; it can usually be compared to their currency.

Because tinnitus can fluctuate daily, it is necessary to obtain an estimate of the variability within a patient before starting treatment.

I would argue that there is a relationship between the magnitude of the tinnitus and a patient's psychological reaction to it. Generally, louder sounds are more annoying. We should not expect the relationship to be perfect. The psychological reaction to the tinnitus will depend on the magnitude and quality of the tinnitus, the individuals' experience with the sound and their overall mood.

Statistics

There are well established principles for determining the number of subjects required in a clinical trial. This 'power analysis' is based on the variables being measured to determine success. Most studies have not used a sufficient number of subjects [14]. Measuring success two years following the termination of treatment, and acknowledging the number and reason for all drops would be helpful.

Persuading your peers you have a reasonable treatment for tinnitus

Abelson [17] proposed some criteria for a persuasive argument that go beyond statistical significance.

Magnitude of the effect

The larger the difference between the control and experimental groups, the more convincing it is that the difference is important.

Specificity of conclusions

If the conclusions are vague, it makes it more difficult to appreciate the significance of the study. For example, a study could show that informational counseling plus cognitive therapy plus retraining therapy is better than informational counseling

only. It would be more powerful to be able to isolate the different factors.

Generality

It is often difficult to know whether a study can be generalized. Can other therapists achieve the same result? Will the treatment work on other patients? If clinicians have to receive special training, the therapy is less convincing. For a treatment to obtain widespread acceptance, it must be shown to be effective in a range of clinics, by different therapists and with different tinnitus populations.

Interestingness

An interesting study is one that changes the way we think about tinnitus. Tinnitus research and therapies will be more interesting if they surprise us in their approach or effectiveness, and if they address an important topic.

Credibility

To be believable, the research must have sound methodology and be coherent with known data and theory. New protocols should either fit within what is currently known about tinnitus, or offer new ways of relating different observations across studies.

Conclusions

Good science will lead to good treatments for tinnitus. This requires a clearly-defined population and an explicit treatment. Tinnitus magnitude and handicap should be measured with established tools. Selecting an appropriate control group is the most difficult challenge. In particular, patient treatments are influenced by patient expectations which need to be carefully considered in the experimental design. Attention to these scientific principles will provide the opportunity for the establishment of effective treatments for tinnitus.

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Can we trust published treatment results?

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Over the years we have all seen inexplicable positive results of tinnitus treatment, particularly with new, unconventional and surprising methods. Such results are often very different from our modest clinical experiences. They are not necessarily conscious falsifications, but may rather illustrate our vain search for new treatments for a basically incurable condition. They may also reflect an early enthusiasm for a new method adopted in an open uncontrolled study. A subsequent controlled study often can not demonstrate any significant results. What is the cause for this? Naturally, the placebo effect contributes, but there are also factors such as variations of tinnitus severity over time, the normal habituation process, mood and the relation to the therapist. There are also factors that influence the therapist, e.g. he/she wants positive results and may have a prejudiced attitude to the actual treatment. So there is reason to have a sceptic attitude to such positive results and raise a number of questions concerning methodology. However, there might also be an opposite attitude that is too negative and the study may reflect another bias of trying to discredit a published method. The best treatment has been tested in a controlled manner and has shown positive results. If controlled studies are not available or not feasible, an open study may be acceptable provided that there are no side effects and it is not unduly expensive. It is likely that such positive results are mostly due to a positive placebo effect. The positive placebo effect is something that the patient may benefit from. We probably need to read tinnitus publications with a critical mind, particularly if the treatment results are unrealistically positive. More discussion and consensus is needed concerning test methodology.

I would like to start with expressing my sincere gratitude for the honour of being selected as guest of honour at this conference. I accept this honour with pride, but I want to state, that I consider it as an appraisal of the tinnitus work that has been done in the department of Audiology at the University hospital in Gothenburg in collaboration with the staff there and with other researchers.

Those of us who have read the tinnitus literature have often been surprised over the strange treatments suggested. To mention a few examples: candle alight in the ear, magnet in the external auditory canal, warm air blown towards drum membrane from fried banana, cotton with aquavit in the ear, blood-sucking leeches behind the ear etc. This may not be too surprising considering the fact that tinnitus is basically incurable. Everything has been tried.

Many of us who have studied the tinnitus literature have also been surprised, encouraged and later disappointed over the excellent treatment results sometimes published also with more commonly accepted methods. Those of us who work in everyday clinics, struggling to encourage and support the distressed tinnitus patients have quite moderate results of our efforts. When we read about the results of others with a very high proportion of

improved and even cured patients we feel that we might have missed something and try to incorporate the new methods in our therapeutic arsenal. Regrettably, most of the times we will be disappointed and frustrated when we do not achieve the excellent results published by others. What did we do wrong? Was the patient selection different? What is the explanation, indeed?

After repeated experiences like that, some of us start to get suspicious that maybe it is not our treatment methods that are incorrect but the reported results of others. This in turn may create an attitude of more or less generalised doubts about new treatment results. I will address some of the explanations and attitudes that are prevailing in these matters.

The guest of honour at the previous international tinnitus seminar was Dr Ross Coles. He gave us a very interesting and thoughtful lecture about the Placebo effect. To me personally this was like a revelation since I had acquired a very suspicious attitude to new treatment results and from my experience there was very little of placebo effects in our controlled treatment studies. To me 'placebo effect' had a negative notion of something like fake and definitely something unwanted that could influence our treatment results in an improper way. Dr Coles

showed us that the placebo effect can also be something desirable which may help and benefit the tinnitus patient.

The Ginkgo Biloba studies

In 1986 a French [1] and a German [2] study both published excellent results with an extract of the leaves of the Ginkgo Biloba tree. It was later followed by another study [3] from Germany with a combination of Ginkgo Biloba and soft laser therapy, equally positive. In these three studies not less than 35, 36 and 20% of the patients were completely cured, i.e. tinnitus disappeared and in an additional 28, 15 and 43% respectively tinnitus improved. This means that 63, 51 and 64% were cured or improved. Such surprisingly positive results are fairly frequently found in open studies. If they were "true", tinnitus treatment would obviously not be a problem. In the relatively few controlled studies there are seldom any statistically significant positive results. So the uncontrolled studies correspond to what often is referred to as "clinical experience".

So we are left with a number of questions not only for clinicians but also for the tinnitus researcher:

How do we explain the surprisingly positive results?

Is the tinnitus literature trustworthy?

Are the positive results reflecting a positive placebo effect?

Are they reflecting the best expectations of the patient?

Are the good results reflecting a pronounced tendency to habituation?

From the methodological point of view further questions could be asked:

Was the study open or controlled? How was the material recruited?

Were only mild cases included and severe cases excluded?

Was there any reason to expect a prejudiced positive attitude from the therapist or the patient to the actual treatment?

Let me speculate a little about the possible explanations for the excellent results.

What influences the patient?

Let us now imagine different factors that might influence the tinnitus patient in a situation of a clinical treatment study. First, the disease course may vary in severity from different causes, e.g. how depressed or stressed the patient is and a natural variation due to the general condition and mood of the patient. An improvement might be recorded during such a positive phase of the symptom. Another possibility is that all tinnitus patients are included and some of the less severe cases may already have habituated but are recorded as improved due to therapy. There are also a number of attitudes of the patient that might influence his

assessment of outcome in a positive direction. The patient might have heard by rumour that a certain treatment is favourable which makes him positive and expectant rather than suspicious or negative. The patient might have heard positive statements about the competence of the therapist, which makes the patient trust him. 'If the therapist says that this treatment is good, I trust him.' Tinnitus is also less annoying if the therapist explains the aetiology and treatment possibilities and the natural habituation process that can be expected. Obviously, the authority, attitudes and charisma of the therapist influences the patient and his evaluation of the actual treatment. If the patient is very worried and stressed by his tinnitus he might also be more susceptible to psychological influences. If the therapist has a particular interest in tinnitus this often means that the patient might receive more consultation time, more visits and more attention than might have been the patient's previous experience. This again might make the patient more positive to the actual treatment. Often the patient may for the first time experience that someone cares about his/her tinnitus. One can also include the so-called Western Electric effect (Hawthorne effect) which means that any change in the actual environment (treatment) may have positive effects. In case of a poor treatment outcome one can also imagine an attitude from the patient as the following: "The therapist has done what he can. I have not improved but why should I make him disappointed? I will tell him that I feel a little better."

There might also be some cultural effects. In certain countries the doctor is held in great, almost god-like estimation and it is important not "to let the doctor lose his face" by reporting negative results of treatment attempts.

Basically, it is each patient's personality and individual reaction to the tinnitus symptom that determines much of the disease course. We must not forget that the patient is very dependent on the therapist's information and caretaking.

What influences the therapist?

Naturally there are also different factors that affect the tinnitus therapist. As a clinician he wishes the patient to improve or hopefully be completely cured. This might induce an attitude, outspoken or not: "When I prescribe this good treatment, I expect You to improve" or "You are improved, aren't You?"

It is naturally preferable that the therapist has his own experience with use of a particular treatment prescribed, hopefully positive. In case of lack of such experience, it might be preferable to refer to other studies with positive results of the actual treatment.

If the therapist wants to perform a tinnitus study it is important that he is not prejudiced. It is important that he does not want to "prove" something, that a method or medication is good or that published treatment modalities are wrong. It is a "feather in the cap" for a therapist to show good treatment results, particularly with a new method.

Remember that we are more likely to report positive results from clinical studies than negative ones. There is also sometimes a risk that the therapist performing a study may have economic advantage by showing that a new medicine or treatment is useful, or the opposite.

Which treatment is most desirable?

It can safely be stated that the therapeutic measure that has been tested in a controlled manner and has shown a statistically significant beneficial effect is also a treatment that could be included in our therapeutic arsenal. However, there are also treatment modalities published in the literature in open studies which have shown good results. Much of those effects are liable to be due to placebo. Such remedies could also be included in our treatment attempts provided that there are no side effects, that the treatment is not unduly expensive and that the published results are explained to the patient. In addition to the unspecific effects of placebo influences and the normal habituation process, it is desirable that any treatment measure also has a specific effect on tinnitus. Let us imagine that the result of a tinnitus study is true or false. We must require that the result is positive and true. If it is positive but false this can be due to the placebo effect or that the study was performed in an open manner. On the other hand, if the result was negative this can be true provided that the study was reliable concerning methodology. I would argue that an open uncontrolled study, properly performed, that is negative can be taken as true and acceptable. However, the study result may also be falsely negative, if there was an improper method adopted, e.g. due to a too small population, wrong patient selection, wrong dosage etc.

So, when we read the tinnitus treatment literature it is important to be aware of these problems.

Evaluation of treatment.

When we read the results of different treatments published there are often a number of questions to raise. It is also understandable that many factors are not always published, maybe because they are not known or maybe because they were not addressed in the study. Examples of this are the degree of severity, of awareness, of annoyance, of influence on concentration and sleep etc. What is the ideal number of questions for assessing the quality and quantity of the patient's tinnitus? How many answer alternatives should be included? If Visual Analogue Scales (VAS) have been used, were they divided in marked millimeters; were leading words written at the scale etc? How often was the VAS recorded? At specific times was the patient describing tinnitus right then or retrospectively etc. How long was the observation period before, during and after treatment?

According to my opinion there is a need for international consensus of such methodological problems and questions.

Reading the tinnitus treatment literature.

On the basis of the above remarks there is reason to have the following questions in mind when we try to evaluate a tinnitus publication particularly if the published results are unrealistically positive:

How were the patients selected?

What was the aetiology of tinnitus?

What method was used to assess tinnitus severity?

Were all patients or only certain patients with a defined severity grading included?

Does the methodology seem correct?

Is the author(s) known for tinnitus research?

Does the report originate from a "reliable" clinic?

Do the results seem too positive?

Were terms such as "cured, improved, unchanged" defined?

Was the treatment controlled and in a blind manner?

Has a positive treatment report found its replication at another centre?

Conclusion

Over the years we have all seen inexplicable positive results of tinnitus treatment particularly with new often unconventional and surprising methods. Such results are not necessarily conscious falsifications, but may rather illustrate our vain search for new treatments for a basically incurable condition. They may also reflect an early enthusiasm for a new method adopted in an open uncontrolled study. Because something is printed and published, it is not necessarily correct. Our evaluation of published results needs to be particularly careful when results are unusually positive. There is reason to have a sceptic attitude to such positive results and raise a number of questions concerning methods and attitudes. However, there might also be an opposite attitude that is too negative and the study results may reflect another bias of trying to discredit a published method. There is a risk of a too sceptic attitude and this attitude may be conveyed to the patient with a less good treatment outcome than if an open-minded or positively encouraging attitude is used when a treatment study is performed. The positive placebo effect is something that the tinnitus patient may benefit from.

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It is important for me to show you briefly the names of those who participated most in the different tinnitus projects: physicians, nurses, psychologists, hearing pedagogues, dentists, physical

therapists, acupuncturist, audiologists, audiological engineers, secretaries, naprapatists and others. Here is the list:

| | | |
|------------------------|--|--------------------|
| Mart Anari | Sven Andersson | Eva Axelsson |
| Marie-Louise Barrnäs | Gunnar Carlsson | Bill Clark |
| Ross Coles | Anette Eliasson | Mats Eriksson |
| Soly Erlandsson | Cecilia Fairall | Gösta Granström |
| Gu Li De | Lillemor Hallberg | Jonathan Hazell |
| Kajsa-Mia Holgers | Björn Israelsson | Kim Kähäri |
| Brenda Lonsbury-Martin | Mark Lutman | Helena Löwen-Åberg |
| Lennart Magnusson | Sune Nilsson | Britt Norinder |
| Deepak Prasher | Inger Pringle | Anders Ringdahl |
| Ulf Rosenhall | Barbara Rubinstein | Agneta Sandh |
| Karin Settergren | Lena Thelin | Birgitta Wahlström |
| Gunilla Zachau | The Tinnitus Association of Gothenburg | |

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Systematic classification of tinnitus

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According to function and anatomy, the following three divisions can be made:

- conductive tinnitus;
- sensorineural tinnitus
- central tinnitus

In the case of sensorineural tinnitus: *sensory tinnitus* can be distinguished from extrasensory tinnitus [15]. In principle, sensory and extrasensory tinnitus include all possible cochlear and neural (auditory nerve) tinnitus models. In order to classify the tinnitus models with respect to the three sensory functional elements, it is deemed best to number them consecutively [17,18]. Thus, tinnitus associated with the first functional element, the cochlear amplification mechanism of OHC, is referred to as *motor tinnitus* [9,11,14,17,19] or *sensorineural tinnitus type I*. Accordingly, tinnitus associated with the electromechanical transduction of the IHCs is designated *transduction tinnitus* [10,20], or *sensorineural tinnitus type II*. Following on from this, the term *transformation tinnitus* [4,5,17,19,20] or sensorineural tinnitus **type III** is used to describe disorders arising during the peripheral signal transfer from the IHCs and along the afferent nerve fibers (synonyms are cochleo-synaptic tinnitus; signal transfer tinnitus). According to this classification, the remaining extrasensory, sensorineural tinnitus mechanisms are referred to as *extrasensory tinnitus* [15] or *sensorineural tinnitus type IV*.

Central tinnitus [1,10,12,16] can be subdivided into: *primary central* and *secondary central* [10] tinnitus. Secondary central tinnitus is based on the fact that conductive and sensorineural tinnitus can only be perceived as such when the peripheral signal is processed in the brain. Mechanisms leading to a response in which the perception of a tinnitus that is first triggered peripherally but then manifests itself in the brain independently of the original source in the ear can be subsumed within the group termed secondary central tinnitus (*centralized tinnitus* or the less scientific, but comprehensible term *phantom tinnitus* are synonyms). The subdivision into primary and secondary central tinnitus therefore concludes every conceivable, central tinnitus model.

Introduction

Recently, a systematic classification of tinnitus generation mechanisms was published [21], which is summarized in this paper.

A broad number of mechanisms, documented in the literature, may cause the symptom tinnitus. Nevertheless, just as one cannot easily deduce the pathophysiology from the symptom hearing loss, the symptom tinnitus alone does not lead to the deduction of the underlying pathomechanism involved in its generation. Even successful treatment modalities such as drug therapies or retraining therapy do not allow to deduce the pathological mechanisms.

In addition there is still no confirmation for the large number of individual mechanisms which supposedly lead to tinnitus.

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Despite this, this lack of knowledge numerous tinnitus models [1,2,3,4,5,7,8,9,10,11,12,13,16,19,20] have been proposed in recent years. In some cases, nearly all forms of tinnitus were already deduced to one single mechanism, e.g. circulatory disturbances.

In order to simplify the current diverse classifications, a systematic approach respecting all anatomical and functional aspects in the generation of tinnitus could be helpful and would allow the incorporation of the various models into this schema.

Material and Methods

The classification is based on current knowledge of auditory anatomy and function.

Figure 1 schematically illustrates the individual functional and anatomical steps involved in sound processing with the middle ear, inner ear and brain. The auditory process begins at the point when

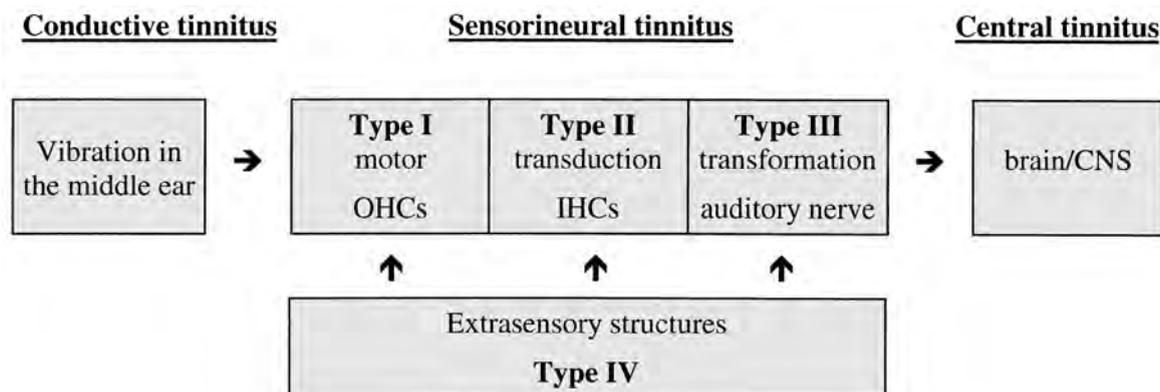


Figure 1 Systematics of possible generation mechanisms of subjective tinnitus, developed from Zenner and colleagues [15,18–20]; conductive tinnitus and sensorineural tinnitus form the peripheral tinnitus.

sound enters the ear and leads to vibrations of the ossicles in the middle ear. These vibrations are directly coupled to the inner ear via the stapes footplate. The *sensorineural* component of the hearing process follows, which comprises three functional and anatomical steps: First, the sound signal is amplified by the *motor of the cochlear amplifier* of the outer hair cells (OHCs); then the amplified signal is transformed into an electrical signal by the final *mechano-electrical transduction* of the inner hair cells (IHCs), which is then transferred synaptically from the IHCs to the afferent nerve fibers as a so-called *transformation* allowing the transfer of the auditory nerve. The sensory functional elements including amplification motor, transduction and transformation are supported by *extrasensory elements* such as the stria vascularis, which is supplied with blood and provides a source of energy. Through the auditory nerve, the transformed signal reaches the *central nervous system (CNS)*, where *perception and cognition* take place.

Results

The systematic classification is based on the conventional division into: *objective* and *subjective* tinnitus.

The anatomical and functional schema in Figure 1 represents a simplified view on the auditory process. Using the same approach, subjective tinnitus can be classified due to its pathophysiological mechanisms.

Concomitant with the anatomical and functional sections of the auditory system, three groups of tinnitus can be distinguished:

- conductive tinnitus
- sensorineural tinnitus
- central tinnitus [12,16]

Sensorineural tinnitus can be further subdivided into four subtypes also based on anatomical and functional units and include all possible cochlear

and neural tinnitus models. The subtypes are numbered consecutively [17,18] and are proposed as: *motor tinnitus* [9,11,14,17,19] or *sensorineural tinnitus type I*. Consecutively, tinnitus associated with the electromechanical transduction of the IHCs is designated *transduction tinnitus* [10,20], or *sensorineural tinnitus type II*. **Transformation tinnitus** [4,5,17,19,20] or *sensorineural tinnitus type III* is referring to disorders arising during the signal transfer from the IHCs and along the afferent nerve fibers (synonyms are cochleosynaptic tinnitus; signal transfer tinnitus). According to this classification, the remaining extrasensory, sensorineural tinnitus mechanisms is described as *extrasensory tinnitus* [15] or *sensorineural tinnitus type IV*.

Accordingly, central tinnitus [1,10,12,16] can be subdivided into *primary central tinnitus* which is pathophysiologically originated in the brain and *secondary central tinnitus* [10]. Tinnitus that is first triggered peripherally but then manifests itself in the brain independently of the original source in the ear can be subsumed within the group termed secondary central tinnitus (*centralized tinnitus* or the less scientific, but comprehensible term *phantom tinnitus* are synonyms). The subdivision into primary and secondary central tinnitus therefore concludes every conceivable, central tinnitus model.

Discussion

Using this approach all known models of the symptom tinnitus can be integrated in one framework.

In table 1 we just classify some common tinnitus disorders with this new classification.

Depending on the course of the disease the type can be further classified as acute, subacute or chronic. The same is possible for diagnostic purposes in which the psychological status, compensated or decompensated, can be registered.

Despite this simplified means, it is clear that there is no single treatment option for all forms of tinnitus.

Table 1

| Classification | Pathogenic models (examples) |
|------------------------|--|
| objective tinnitus | glomus tumor, angiostenosis, protruding bulbus, jugular vein |
| subjective tinnitus | |
| conductive tinnitus | disturbance of tubal ventilation, middle ear myoclonia |
| sensorineural tinnitus | |
| type I | hypermotility, DC tinnitus, edge effect tinnitus, efferent tinnitus caused by regulatory disturbances of the nerves, noise trauma, ion channel disorders of the outer hair cells |
| type II | continuous depolarization of ion channel disorders of the inner hair cells, disturbance of the stereocilia of the inner hair cells |
| type III | release of transmitters, flooding with synaptic transmitters, swelling of the afferent nerve fibers, excitotoxic tinnitus |
| type IV | disorders (e.g. of the ion channels) of the stria vascularis, circulatory disorders of the cochlea, resorption disorders and osmolarity change of endolymph, endolymph hydrops |
| central tinnitus | |
| primary | brain tumors, multiple sclerosis, closed head trauma |
| Secondary | Phantom tinnitus |

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Computer simulation of a tinnitus model based on labelling of tinnitus activity in the auditory cortex

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We used noise trauma and different doses of salicylate to induce a hearing deficit and increased spontaneous activity in the auditory cortex of awake gerbils as revealed by 2-Deoxyglucose method and c-fos-immuno-cytochemistry. Evidence that the increased spontaneous activity in treated animals is due to tinnitus comes from the observation that the auditory brainstem of the same animals is not or only weakly activated. This rules out that the measured cortical activity reflects external noise and or originates from the cochlea or the brainstem. In addition, neuronal activity in the limbic system was strongly correlated with the cortical tinnitus activity. Based on a correlation analysis of these observations a computer model was developed. It is designed to explain how a decreased auditory input, due for example to a peripheral hearing deficit, may decrease spontaneous activity in the brainstem and give rise to increased activation of the auditory cortex. In this line of reasoning, the cortical activation is a consequence of neuronal mechanisms counteracting the cochlear hearing deficit. Key elements of the model are lateral inhibition, positive feedback, and plastic changes of feedback under command of the limbic system. According to the simulation tinnitus activity would not be generated without lateral inhibition while its strength and persistence completely depend on plasticity, strength, and persistence of auditory feedback mechanisms.

Introduction

Subjective tinnitus is an annoying auditory percept which does not have an acoustic source in the environment or in the body. Although many people suffer from such phantom sounds, there is no objective method for detecting or evaluating the severity of a tinnitus and up to now it can be treated only with limited success. It seems to be still the most discussed presumption that tinnitus is generated by cochlear mechanisms, like hyperactivation of hair cells [1,2]. However, the highest success rate for a therapy has been reported from the so-called 'tinnitus retraining therapy' which is actually based on assumptions about central auditory processing and aims at habituation of tinnitus perception [3-6].

Our results also strongly support central mechanisms of tinnitus generation: provided our animal model holds for the human brain the perception of subjective tinnitus is based on hyperactivity in the brain itself. High doses of salicylate (aspirin) and noise trauma (shotguns, fireworks) are known to cause at least transient hearing deficits [7] and often also tinnitus in humans and animals [8]. We used

the 2-Deoxyglucose technique and c-fos immunohistochemistry in gerbils to study the consequences of hearing deficits caused by different doses of sodium salicylate or by impulse noise in the central nervous system [9-12]. A statistical analysis of c-fos labelling in different auditory and non-auditory brain areas indicated correlations of tinnitus related activities, a central role of the auditory cortex in tinnitus genesis, and interactions between auditory and limbic structures. These observations were used to define constraints for a computer model for a central generation of tinnitus activity.

Methods

In order to produce tinnitus, awake gerbils (*Meriones unguiculatus*) were treated with different doses of sodium salicylate. Alternatively, a transient hearing deficit accompanied by tinnitus was induced by means of a toy pistol fired close to each ear. Activity in all brain areas of the gerbil was surveyed with the ¹⁴C-2-deoxy-fluoro-D-glucose (2-DG)-method and with c-fos immuno-cytochemistry (for more details see [9,11] and Wallhäusser-Franke and Langner, this volume).

The counts of c-fos labelled neurons in different

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brain areas were used for defining a correlation matrix of the underlying neuronal activities in the dorsal cochlear nucleus, inferior colliculus (IC), the main auditory cortex areas AI and AAF, and lateral (LA), medial (MeA) and central amygdala (CeA). In addition, the data were examined using a principal component analysis (iterated principal axis, varimax rotation, program Systat 7.0) and multidimensional scaling (Guttman loss function, program Systat 7.0).

The results motivated the design of a computer model for tinnitus genesis. The input layer of the model was designed as a one-dimensional array of integrate-and-fire neurons along the tonotopic axis representing the auditory nerve in a highly simplified manner. Several hierarchical organized layers were supposed to represent higher order nuclei with functions reduced to sharpening of frequency tuning by lateral inhibition and with positive feedback 'at the cortical level'. Lateral inhibition or a loss of inhibition was proposed already previously as essential components of models for a central tinnitus genesis [13,14]. In addition, plasticity, strength, and persistence of the feedback was hypothesized in the present model to be under control of non-auditory inputs, especially from the limbic system, and therefore implemented by free parameters in the simulation.

Results

Labelling of tinnitus related activity

With increasing doses of salicylate, the observed 2-DG-labelling due to spontaneous activation decreased in the cochlear nucleus and in the inferior colliculus. In contrast, we observed an increase of 2-DG-activity in the auditory cortex of the same animals. Because excitation of cochlear hair cells or increased spontaneous activity in the auditory nerve should activate also the auditory brainstem, our findings exclude the possibility that the salicylate or noise-evoked spontaneous activity found in the cortex of the gerbil originates in the cochlea.

The auditory cortex was also the *only auditory* region which exhibited an increased number of immuno-reactive neurons after salicylate treatment which increased proportional to the salicylate dose. Similarly, we found a dose-dependant increase in the central nucleus of the amygdala and the pre-frontal cortex [15].

Since salicylate, in addition to inducing a hearing deficit, is known to influence the brain directly, noise trauma was used as additional paradigm. Several hours after the impulse noise the auditory cortex, especially the anterior field AAF revealed high 2-DG-activity even in cases where it was wiped out completely in the inferior colliculus. In addition to this increase in metabolic activity an increased number of *immuno-reactive* neurons was found in the auditory cortex, mainly in AAF [16]. As a consequence of the noise trauma also neurons in areas which receive efferents from the auditory cortex, the dorsal cochlear nucleus (DCN) and the inferior col-

liculus, were found to be immuno-reactive: In contrast, the ventral cochlear nucleus being free from direct cortical feedback did not reveal any c-fos labelling.

In addition to the increased number of immuno-reactive neurons in cortical auditory areas after impulse noise, there was increased reactivity in the lateral, medial and central nucleus of the amygdala complex.

Statistical analysis of c-fos activity

A correlation analysis of c-fos activity in 9 awake animals 0, 1, 3, 5 and 7 hours after noise-trauma was performed using the numbers of labelled neurons in DCN, IC, AI, AAF, and lateral, medial and central amygdala. As illustrated in Figure. 1 there was a medium sized correlation between AI and AAF (0.7), while the activity in each of these major auditory cortex field was highly correlated with a particular part of the amygdala. The strongest correlation was obtained between AI and the lateral amygdala (0.99) and the second strongest between AAF and the central amygdala (0.92).

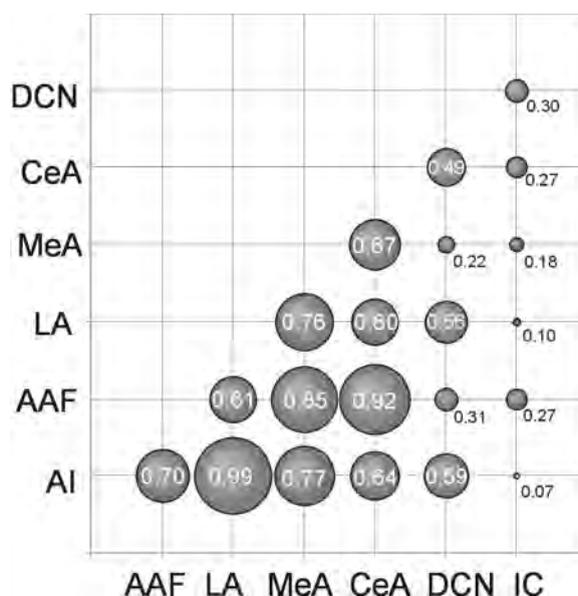


Figure 1 Pearson correlation matrix of c-fos activity after noise trauma.

Correlation of counts of c-fos labelled neurons in auditory areas DCN, IC, AI, and AAF and nuclei of the amygdala complex, i.e. lateral (LA) medial (MeA), and central amygdala (CeA) measured at several hours after noise trauma. The Pearson correlation coefficient is indicated by the diameter of the circles and given by the corresponding numbers. Note, the high correlation of activities in AI and LA on one hand and AAF and MeA - CeA on the other hand. Note, also the low correlation of the low activities in DCN and IC with that in all other areas.

The figure is based on the same data as demonstrated in Figure 1. All correlation coefficients above 0.26 between each pair of the observed activities is indicated by the thickness of the connecting

arrows and the corresponding numbers. The resulting lines do not express direct anatomical connections. However, they suggest that AI and AAF communicate with the amygdala via different ways. According to this figure it is tempting to speculate that perhaps AI provides a major input to the amygdala, while AAF (indirectly) receives output information.

In Figure 2 the correlations are used for a scheme of neural interactions. Although no assumption about direct connections between different areas can be derived from such schemes, it nevertheless suggests different roles for AI and AAF with respect to their communication with the amygdala and the lower auditory nuclei.

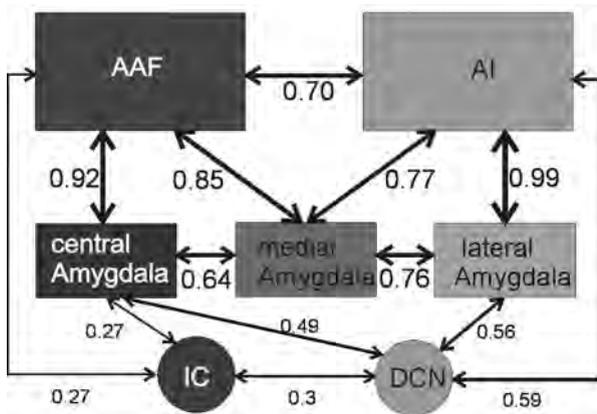


Figure 2 Correlation of c-fos activity after noise trauma.

A principal component analysis revealed three major components explaining together 83% of the total variance (Figure 3). The first component (36% of the variance) is composed mainly of activation in AI, LA, and MeA. The second component (30% of the variance) is composed of AAF, CeA and MeA activity, while the third component is mostly defined by the DCN activity.

The result of a factor analysis is demonstrated by

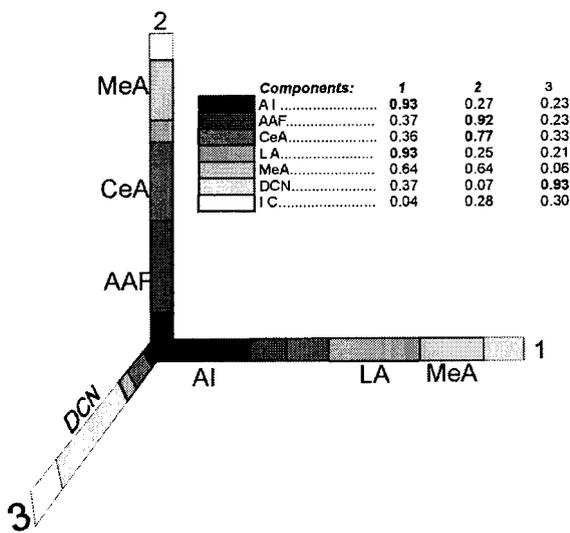


Figure 3 Components of factor analysis of c-fos activity after noise trauma.

a matrix and in shape of 3-dimensional coordinate system. As might be expected from the correlation analysis (see Figure 1) the three major components of the tinnitus related activity may be defined as mostly a combination of (1) AI, LA, and MeA, (2) AAF, CeA, and MeA and (3) a smaller component dominated by DCN activity.

As a result of a multidimensional scaling the central role of AI for the expression of c-fos activity after noise trauma becomes obvious. The filled circles on the right side of the resulting circumplex represent auditory fields, while the amygdala nuclei group together on the other side. The result (visualized by the connecting lines) suggests that AI is interacting in a similar way with all observed auditory and non-auditory areas and therefore may be the center of the observed tinnitus related activity.

Finally, a multidimensional scaling revealed the special role of the primary auditory cortex AI as demonstrated by its position in the center of a circumplex (Figure 4). Note, the functional meaningful order of the configuration with auditory nuclei on one side and nuclei of the amygdala complex on the other side of the circumplex. Although DCN and IC are only weakly activated the result of the analysis suggests that their activity is nevertheless related to the central tinnitus activity.

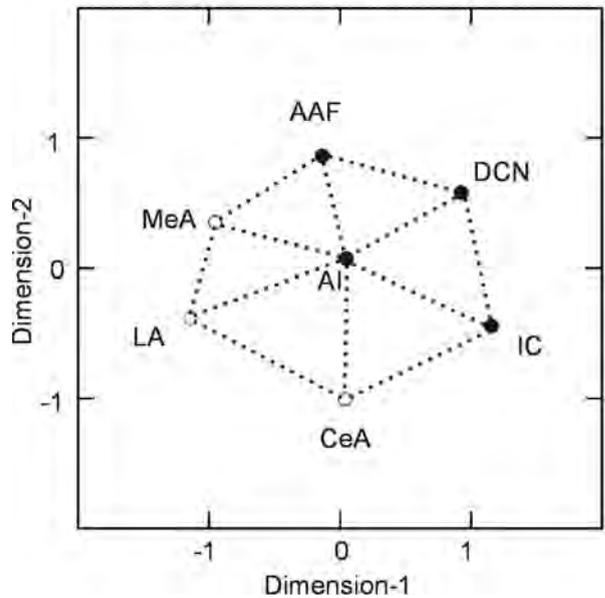


Figure 4 Multidimensional scaling: Circumplex of c-fos activity after noise trauma.

Results of a computer simulation

As demonstrated in Figure 5 a hierarchical organized network simulating major aspects of the auditory system, including tonotopy, lateral inhibition and positive feedback may explain the genesis of tinnitus. The simulation (Figure 6) suggests that tinnitus may result from the attempt of the central auditory system to account for a peripheral hearing deficit. Lateral inhibition enhances edges, peaks, and dips in the hearing threshold which may appear

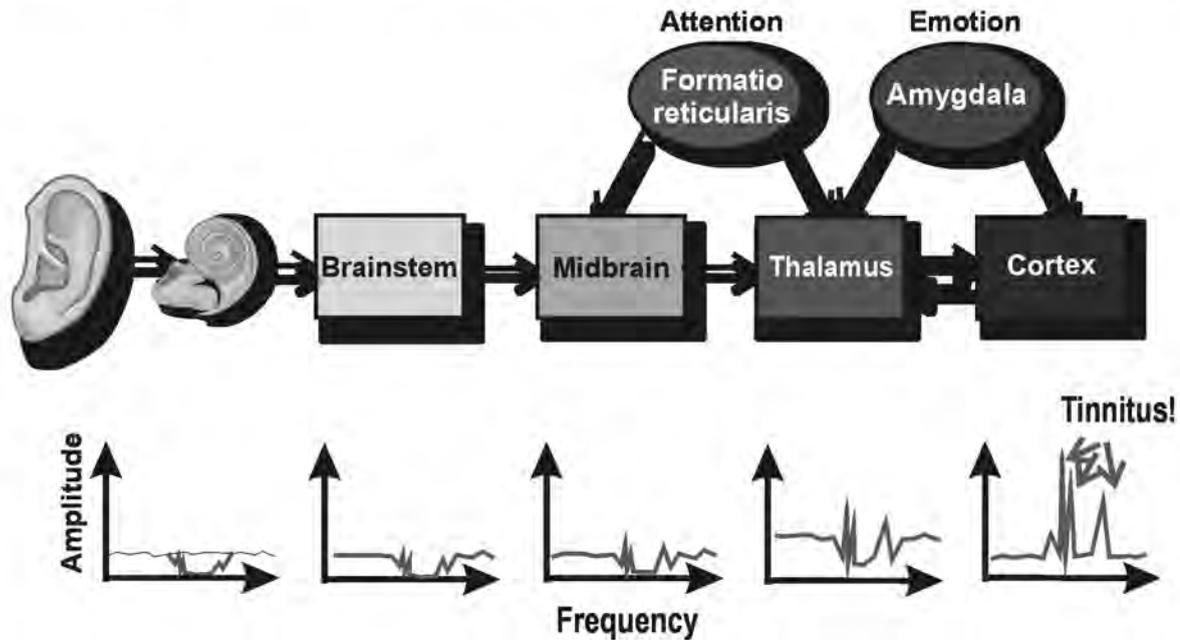


Figure 5 A model of tinnitus genesis in the central auditory system.

in consequence of a hearing deficit. Focussing attention on these weak activities is supposed to result in a localized increase of positive feedback which may amplify spurious activities up to levels limited only by neuronal saturation (Figure 6 B). The feedback mechanisms responsible for this amplification are under control of the neuronal systems related to attention and emotion (formatio reticularis, locus coeruleus, amygdala). Assuming that the parameters of feedback (strength and frequency extent) are altered by plastic changes, tinnitus activity may persist also without auditory input or peripheral spontaneous activity (Figure 6 C).

The figure is supposed to describe the basic idea underlying the computer simulation. A peripheral hearing deficit is transferred into central brain activity as a reduction of activity along the neural frequency axis. Under control of the amygdala and formatio reticularis (and probably also other neural structures) the central auditory gain control attempts to compensate for the reduced activity. Overcompensation, especially of frequency ranges near the border of the hearing deficit which are emphasized by lateral inhibition result in tinnitus activity at the level of the cortex.

(A) The curves represent the input activity and a distorted peripheral threshold (or transfer) curve along a hypothetical frequency axis. The absolute position along the y-axis is unimportant.

(B) The lowest curve shows the response of a medium layer ('IC') of the model with only small enhancements at the borders of the 'hearing deficit' due to lateral inhibition. However, the next curve shows a peak at the lower border resulting from positive feedback in the area of the hearing deficit. In this case there is no peak at the upper border, because lateral inhibition was selected to function only from high to low frequencies. (C) Now the

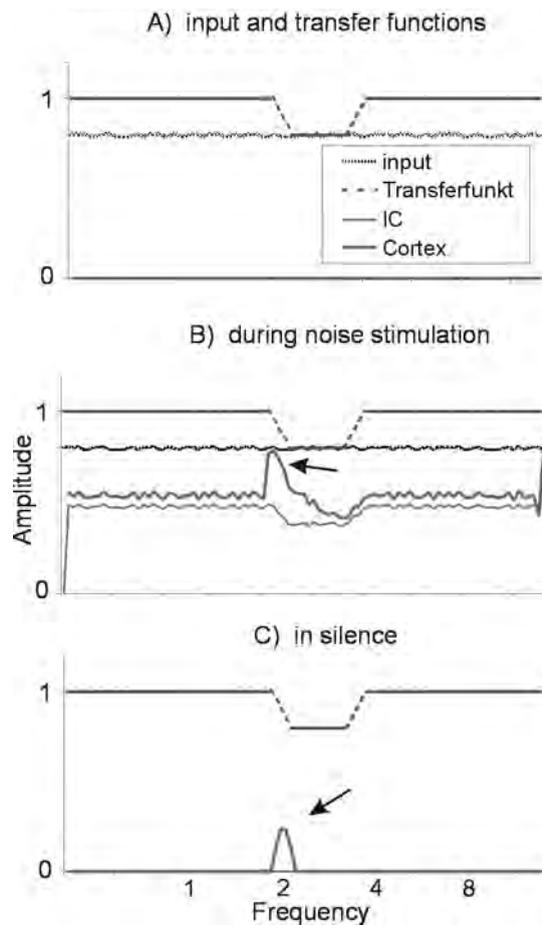


Figure 6 Simulation of tinnitus generation.

input activity was switched off. As a result all responses go down except in the frequency range where 'plasticity' provides ongoing increased positive feedback and therefore 'tinnitus'.

Discussion

The main results of our experiments applying traumatic amounts of salicylate or noise on gerbils were decreased spontaneous activation of the auditory brainstem indicating a substantial hearing loss concomitant with high activation of the auditory cortex. As excitation of cochlear hair cells should activate all parts of the auditory brainstem, these findings exclude the possibility that the salicylate or noise-evoked increased spontaneous activity found in the cortex of the gerbil originates in the cochlea. After inducing a noise trauma the counts of c-fos labelled cells in the DCN and the IC were also slightly increased supporting previous electrophysiological studies of increased spontaneous activity in these nuclei [17,18]. Since the ventral cochlear nucleus is not activated, we believe that labelled cells in the DCN and the IC are due to efferent activation from the cortex. According to these arguments, for our animal model hyperactivation of cochlear hair cells can be rejected as a mechanism responsible for tinnitus generation. Instead, the decreased input into the central auditory system seems to give rise to compensational mechanisms in the central auditory system which include interaction of neuronal excitation and inhibition as well as feedback loops between different parts of the auditory system. This may result in neuronal oscillations and overcompensation of the thalamocortical system causing an increase of central spontaneous activity (Figure 6).

A statistical analysis of differential effects in different auditory and non-auditory areas at different times after noise trauma supports these assumptions. It suggests a central role for tinnitus genesis of the auditory cortex and a strong influence of the limbic system, especially the amygdala which is known to be activated during emotional situations of arousal and stress.

In accordance with clinical [19] and own [20] observations, the computer simulations suggest that peaks along the slope of an impaired threshold curve may give rise to a cortical hyperactivity. It is obvious that in the range of these typical tinnitus frequencies relatively little damage should exist in the cochlea and that also spontaneous activity in the auditory nerve would be normal [21]. It seems that in contrast to peripheral models of tinnitus genesis for our model it is essential that spontaneous activity in the auditory nerve is suppressed and not enhanced. However, at a closer look the really important fact is that the spontaneous activity along the tonotopic axis shows irregularities like peaks or dips which will be enhanced by central processing through lateral inhibition. Another property of the simulation is that it can create long lasting 'cortical' activity even in the absence of spontaneous activity providing input from the auditory periphery. However, for the persistence of these activities the model requires plastic changes in positive feedback loops. Positive feedback mechanisms were recently demonstrated in bats [22], while plasticity seems to be a common characteristic of the cortex presumably

involved in tinnitus mechanisms as well [23]. Feedback from the cortex may explain the emergence of various tinnitus sounds as the cortex contains maps for a variety of stimulus parameters [24,25]. The computer simulation allows for a role of the limbic system by the parameters controlling lateral inhibition and strength and plasticity of the feedback.

Conclusions

- A statistical analysis of our experimental findings suggests that as result of overcompensation of a peripheral hearing deficit by the central auditory system spontaneous activity in the cortex may increase dramatically.
- Therefore, the cortical hyperactivity, which may be perceived as tinnitus, arises in the central nervous system itself.
- Attention, emotion, and stress may be involved, because the limbic system may be responsible for the control of lateral inhibition, feedback and plasticity which according to a computer simulation are involved in tinnitus genesis.

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Pathophysiology of severe tinnitus and chronic pain

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Current hypotheses of the pathophysiology of chronic pain and some forms of severe tinnitus assume that the pain and the tinnitus are phantom sensations that are caused by changes in the function of the central nervous system, which occur as a consequence of the plasticity of the nervous system. Neural plasticity allows novel input or deprivation of input to change the function of specific parts of the central nervous system. Such changes may result in symptoms such as severe tinnitus or chronic pain and altered perception of normal auditory and somatosensory stimuli.

Novel input from the peripheral nervous system can result from tissue damage or injury to peripheral nerves. Somatic stimulation that normally is innocuous may become painful (allodynia) and an overreaction to painful stimulation (hyperpathia) may occur. Similarly, many individuals with severe tinnitus may experience an abnormal perception of loudness (hyperacusis) similar to allodynia. The abnormal perception of loudness often associated with severe tinnitus is usually referred to as hyperacusis. It might be more adequate to use the term phonophobia for that kind of abnormal perception of sounds because it is usually described as an adverse reaction rather than a perception of sounds being more loud than perceived by the general population [1]. As is the case for chronic pain it is believed that these changes in function may occur as a result of neural plasticity and deprivation of input or overstimulation. These changes in function also may alter temporal integration of painful stimuli. The changes in the nervous system consist of reduction of inhibition at the segmental level and a redirection of somatic input as a result of changes in synaptic efficacy. Studies in animals have shown that deprivation of auditory input or overstimulation can alter temporal integration of auditory stimulation in a similar way.

The changes in the function of the central nervous system that cause chronic pain and severe tinnitus are not associated with morphologic changes that can be detected by known imaging techniques but the areas of the brain that are activated can be identified by functional imaging tests. Few electrophysiologic or behavioral tests are abnormal in individuals with chronic tinnitus and chronic pain, which complicates the diagnosis of tinnitus and the ability to monitor progress of treatment. The clinician mainly has to rely on the patients reported symptoms.

Introduction

It was perhaps in the field of pain research that it was first recognized that even severe and debilitating conditions such as chronic pain may arise from functional changes in the function of the central nervous system without any detectable morphologic abnormality being present. Similarly, during the past 2 or 3 decades, it has become increasingly evident that diseases such as severe tinnitus are not always associated with detectable morphologic changes but instead the symptoms are caused by a functional reorganization of parts of the central nervous system that occur because the nervous system is plastic.

Severe tinnitus is usually defined as tinnitus that interferes with sleep, work and social life. In most cases, severe tinnitus is believed to be caused by

changes in the function of the central auditory nervous system. However, some forms are caused by changes in the function of the cochlea, as evidenced from the fact that severing the auditory nerve can relieve tinnitus in some individuals. This indicates a peripheral location of the abnormality that caused the symptoms of tinnitus. Similarly, acute pain is probably generated locally as a result of trauma, inflammation etc., but chronic pain that may follow acute pain or appear without any known cause is in most instances generated by abnormal function of the central nervous system.

Acute somatic pain has two components, a fast response that results from activation of touch receptors and a slow and delayed response that results from activation of specific pain receptors (nociceptors). The fast response is carried by pathways of the somatosensory system and the slow response is mediated through specific pain pathways.

Several disorders of motor and sensory systems

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can be caused by functional changes in the nervous system. Previously, the term “non-organic” or “functional” was used to describe disorders that were regarded to be psychological in nature. It is important to note that it is now established knowledge that disorders that have no detectable morphologic correlate can be caused by physiologically verifiable changes in the function of parts of the central nervous system. The diseases that are caused by such changes in the function of the nervous system have many similarities and in this article we will specifically discuss the similarities between severe tinnitus and chronic pain.

Comparison of symptoms and signs of tinnitus and chronic pain

The perception of a sound without any physical sound stimulating the ear is comparable to somatic sensations that occur without a physical stimulus. The most convincing evidence that such abnormal sensations are caused by functional abnormalities in the central nervous system comes from the sensations and pain that are referred to an amputated limb or the tinnitus that occurs after the auditory nerve has been severed. However, many other forms of chronic pain and tinnitus have similar causes and are known as phantom sensations [2].

Both severe tinnitus and chronic pain are associated with other abnormal sensations of innocuous and noxious stimulation and both conditions are often associated with changes in the temporal integration of sensory and painful stimuli. Individuals with chronic pain often perceive innocuous stimuli as pain (allodynia) and somatic stimulation that normally causes acute pain may give an exaggerated pain response, which lasts beyond the stimulation (hyperpathia). Similarly, individuals who have severe tinnitus also often have hyperacusis and strong sounds often give a sensation of pain. Many individuals with severe tinnitus perceive ordinary sounds to be unpleasant or painful, thus similar to allodynia. Sounds often have emotional components in such individuals, yet another similarity with chronic pain.

Temporal integration

Chronic pain is often accompanied by altered temporal integration. Normally, temporal integration manifests as a decrease in threshold with increasing duration of a stimulus, or increased strength of the perception of a stimulus when its duration is increased. It can be described as a system’s memory – how the response to one stimulus is affected by a previous stimulation. Temporal integration of stimuli that are perceived to be painful are altered in individuals with chronic pain [3] (Figure 1).

As a sign of temporal integration, the threshold for pain from electrical stimulation of the skin normally decreases when the stimulus rate is increased (Figure 1A). In patients with chronic pain, the threshold for pain from electrical stimulation is

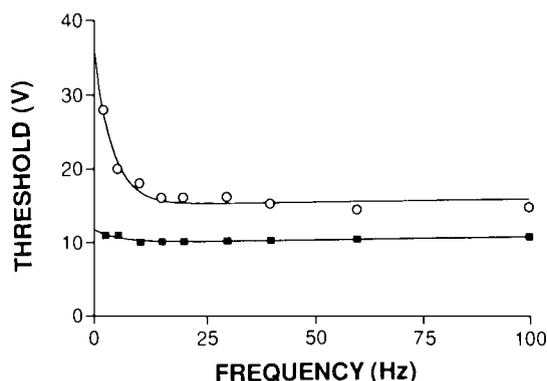


Figure 1 (A) Threshold of sensation (filled squares) and pain (open circles) from electrical stimulation of the skin on the forearm shown as a function of stimulus repetition rate in an individual without pain. The solid line is an exponential function fitted to the experimental data points. (B) Similar graph as in A, showing results from an individual with chronic pain. (From Moller and Pinkerton, 1997, [3].)

lower than it is in individuals without pain and it decreases much less with increasing stimulus rate, or not at all, indicating that temporal integration is reduced or absent (Figure 1B) [3].

In experiments in cats, Gerken [4] showed that the behavioral threshold to electrical stimulation of the cochlear nucleus decreased when the number of stimuli was increased thus an indication of temporal integration. After noise exposure that caused hearing loss of approximately 50 dB, the threshold was much lower and it did not decrease noticeably when the number of stimuli was increased. That means that sound deprivation has increased the sensitivity of the auditory nervous system and eliminated the temporal integration of input (electrical stimulation) to the auditory system. These findings support the hypothesis that some forms of chronic pain and severe tinnitus are caused by specific changes in the function of the nervous system.

Current hypotheses about generation of pain and tinnitus

The question about where pain or tinnitus is generated and how it is generated has been the subject of considerable research effort. There is considerable evidence that at least some forms of chronic pain and tinnitus are generated in the central nervous system. The strongest sign is probably phantom limb syndrome for pain and tinnitus with severed auditory nerve. The symptoms and signs of severe tinnitus and chronic pain can be explained by altered excitability of certain parts of the central nervous system. Hearing disorders that normally were regarded as being caused exclusively by injury to the cochlea, such as noise induced hearing loss, have now been shown to include noticeable changes in the function of the auditory nervous system [5]. These changes in the central nervous system are now believed to be the consequences of neural plasticity.

It has been hypothesized that the symptoms of chronic pain are related to an altered function of the wide dynamic range (WDR) neurons that receive input from pain receptors and different somatosensory receptors [6–9]. These WDR neurons normally convey somatosensory information to the somatosensory cortex through the ascending somatosensory pathways. The change in the function of these neurons can occur as a result of increased excitatory input from pain fibers or because of a reduction of inhibitory input (Figure 2). Abnormal input such as that generated from tissue injury may cause such changes in the function of the WDR neurons. The hypothesis that abnormal neural activity generated by trauma can cause phantom pain is supported by the finding that the phantom limb syndrome can be avoided by blocking the neural conduction in the peripheral nerve that leads to the limb to be amputated by a local anesthetic before the operation [10]. Denervation, thus causing deprivation of input, can also cause pain and other abnormal sensations associated with changes in the function of the central nervous system.

The fact that normally innocuous sensory stimulation may be perceived as painful sensations in individuals with chronic pain (allodynia) means that information has been re-routed from the somatosensory system to pain circuits as the information ascends through the central nervous system. That may be caused by increased excitability of these WDR neurons. The re-routing of innocuous somatosensory information to pain pathways that cause allodynia can also be explained with increased excitability of the WDR neurons where the increased excitability may open synapses that normally are dormant. Wall already in 1977 [11]

suggested that this might occur in individuals with chronic pain.

These hypotheses were developed to explain pain caused by tissue damage and injury to peripheral nerves [6,8]. Similar hypotheses have been presented to explain other kinds of chronic pain such as face pain (trigeminal neuralgia) [12]. Not all people with the same tissue injury develop chronic pain, and therefore it can be assumed that other factors are necessary in order for chronic pain to develop.

Several aspects of tinnitus can be explained in a similar way as the changes in the function of the WDR neurons can explain the symptoms of chronic pain. It seems likely that increased excitability of auditory nuclei may result from abnormal stimulation or deprivation of stimulation. Thus, there is considerable evidence that overstimulation and deprivation of input from the cochlea to the auditory pathway can lead to increased sensitivity of the central auditory nervous system. Evidence has emerged recently that most forms of cochlear damage can cause functional reorganization of the auditory nervous system. For example, noise induced hearing loss has been shown to cause morphologic changes in the auditory nervous system [13]. Cochlear hearing loss causes deprivation of input to the auditory system and the subsequent changes that occur in the auditory nervous system as a result of cochlear damage are thus believed to be a result of sound deprivation. Thus, changes similar to those that have been postulated to explain symptoms of chronic pain may explain features of severe tinnitus.

Similar to the re-routing from the somatosensory system to pain circuits that is believed to occur in some individuals with chronic pain, evidence has been presented that information in the classical ascending auditory system may be re-routed to the

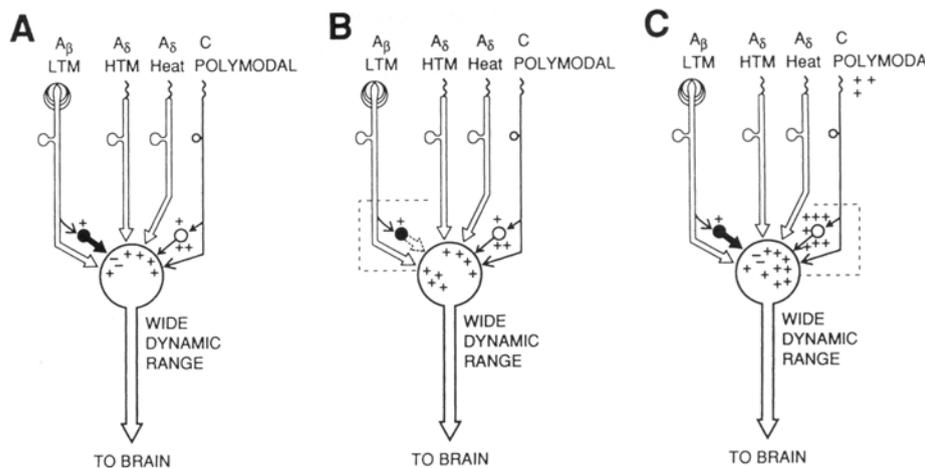


Figure 2 Illustration of the hypotheses that show how changes in the function of WDR neurons may lead to chronic pain.

A: Normal innervation of WDR neurons. Large circles: Sensory transmission, small open circles with + signs: facilitatory interneurons, filled circles and - signs: inhibitory interneurons.

B: Loss of inhibitory controls from A β afferents.

C: Exaggeration of facilitatory mechanisms activated by C polymodal afferents.

LTM: Low-threshold mechanoreceptor afferent, HTM: High-threshold mechanoreceptor afferent. (From Price *et al.*, 1992 [8].)

non-classical auditory system in some individuals with severe tinnitus [14].

Where is central tinnitus generated?

The anatomical location of the nuclei that become hyperactive is not known precisely but some studies indicate that the inferior colliculus (IC) is involved in tinnitus and hyperacusis (phonophobia) yet it may be different for different forms of tinnitus. Thus, intracranial recordings from patients undergoing microvascular decompression operations for severe tinnitus do not show any noticeable difference in the responses from the auditory nerve and the cochlear nucleus compared with patients with similar hearing loss who were operated for trigeminal neuralgia. The latency of evoked potentials recorded from the inferior colliculus were slightly shorter than in individuals with the same hearing loss but no tinnitus, although not statistically significant [15]. That indicated that the location of the abnormality was central to the cochlear nucleus and hinted that the IC might be involved. These findings are in good agreement with animal experiments that showed that the spontaneous activity in auditory nerve fibers is little affected by administration of salicylates but the spontaneous activity of neurons in the central nucleus of the ICC increased after administration of salicylate [16]. Studies by Chen and Jastreboff [17] showed increased spontaneous discharge rate in neurons on the external nucleus of the IC (ICX) after administration of salicylates in rats. Other studies found evidence that exposure to loud sounds in animal experiments reduced GABAergic inhibition in the IC [18] and that changed the temporal integration of sound in the IC.

These findings support the hypothesis that the anatomical location of the physiologic abnormalities that cause severe tinnitus is not the ear, the auditory nerve or the more peripheral parts of the ascending auditory pathway. There are also several indications that the neural activity that produces the sensation of tinnitus is generated in other parts of the central auditory nervous systems than those that normally process auditory information. Several studies have shown evidence that some forms of severe tinnitus are generated in the non-classical ascending auditory pathway rather than the classical pathway that normally process auditory information [14]. The non-classical ascending auditory pathway as been described as consisting of two systems, the diffuse system and the polysensory system [19]. Neurons in the non-classical auditory systems are not sharply tuned as they are in the classical auditory system [20](Aitkin) and neurons in the polysensory system receive both inhibitory and excitatory input from other sensory systems. The non-classical auditory system projects to secondary auditory cortical areas rather than the primary cortical areas and it connects with many other regions of the brain such as the brainstem reticular activating system, association cortices and the limbic system. Little is known about the role of the non-

classical auditory system under normal conditions, however its projections indicate it may be involved in sensations of emotion and pain.

The hypothesis that the non-classical (polysensory system) may be involved in generation of tinnitus is supported by studies, which showed that the perception of tinnitus in some individuals with severe tinnitus could be manipulated by activation of the somatosensory system (electrical stimulation of the median nerve [14]). The effect was noticeable in 10 of the 26 individuals with severe tinnitus that were studied. Four perceived their tinnitus stronger during the electrical stimulation and 6 perceived the tinnitus less intense. Sixteen did to detect any change. That some of the people studied perceived their tinnitus stronger and some perceived it to be weakened by activation of the somatosensory system in agreement with the finding that the somatosensory input to some neurons are facilitatory and some input is inhibitory to neurons in the polysensory auditory system. Electrical stimulation of the median nerve did not noticeably affect the perception of sounds in individuals without tinnitus, except for strong sounds that were perceived as unpleasant, where electrical stimulation of the median nerve reduced the perceived intensity by a small amount. The manipulation of the perception of tinnitus by stimulation of the median nerve may be similar to manipulating chronic pain by electrical stimulation of the skin (TENS).

The involvement of the non-classical auditory system in severe tinnitus indicates that the external nucleus of the IC (ICX) could be the anatomical location of the abnormal neural activity that produces tinnitus. The ICX receives its input from the central nucleus of the IC (ICC) and it is the main connection between the classical ascending auditory system to the non-classical pathway. Also animal studies support the hypothesis that the non-classical auditory nervous system is involved in tinnitus. Recent studies by Eggermont and co-workers [21] supported the theory that the non-classical auditory system is involved in tinnitus. These investigators showed that the spontaneous discharge rate of cells in the secondary auditory cortex (AII) increased in guinea pigs after administration of salicylate, while the discharge rate of neurons in the primary auditory cortex (AI and AAF) was little affected.

Other studies support the hypothesis that tinnitus is not (always) caused by neural activity in the classical auditory system. Thus, imaging studies in individuals who can voluntarily alter their tinnitus have shown that the neural activity in the cerebral cortex that is related to tinnitus is not generated in the same way as sound evoked activity [22].

Similarities with other hyperactive disorders

Similar alterations in the central nervous system as occur in individuals with severe tinnitus and chronic pain have been shown to occur in hyperactive disorders of motor systems. For example, the facial motonucleus in individuals with hemifacial spasm (HFS) is hyperactive. HFS is a rare disorder

that in addition to spasm also includes synkinesis. Studies have supported the hypothesis that the hyperactivity and synkinesis in HFS are the result of plastic changes in the nervous system that are caused by simultaneous occurrence of several factors, one of which is irritation of the facial nerve from close contact with a blood vessel [23]. Animal experiments have shown that repeated electrical stimulation of the peripheral portion of the facial nerve can cause such hyperactivity to develop [24]. Other studies have shown that close contact with a blood vessel alone is not sufficient to cause the development of such hyperactivity but simultaneous slight injury to the facial nerve at the location of the close contact with a blood vessel is necessary to cause signs and symptoms of hyperactivity to develop [25]. These studies support the hypothesis that several conditions must be fulfilled in order that symptoms may become evident.

Conclusions

It has become increasingly evident that plastic changes in the central nervous system play an important role in many different disorders. An increasing number of studies show evidence that chronic pain and some forms of severe tinnitus are associated with functional changes in the nervous system. These functional changes are the cause of the symptoms and signs of these disorders. Similarities have also been identified with other forms of hearing disorders and with hyperactive disorders such as various forms of spasm. There is mounting evidence that the effect of plastic changes in the auditory nervous system may contribute to forms of hearing loss that have traditionally been associated with cochlear lesions [5]. Re-routing of information in the brain due to deprivation of input, altered input or overstimulation seems to be a much more common phenomena than earlier believed. That the same abnormal input does not cause signs of pathology in all individuals may be explained by assuming that other yet unknown factors are necessary in order that these functional changes may occur.

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The neurophysiological model of tinnitus and hyperacusis

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The neurophysiological model of tinnitus and hyperacusis resulted from analyses of clinical and research data on tinnitus from the perspective of the basic functional properties of the central nervous system (CNS). The observation that tinnitus induces distress in only about 25% of the people perceiving it, with no correlation between the distress and the psychoacoustical characterization of tinnitus, and that the psychoacoustical characterization of tinnitus in the population of patients suffering from it is not related to the severity of tinnitus and to the treatment outcome, argued strongly that the auditory system is only a secondary system, and other systems in the brain are dominant in clinically-relevant tinnitus. Moreover, experiments by Heller and Bergman showed that the perception of tinnitus cannot be pathological, since essentially everyone (94% of people without tinnitus experience tinnitus when isolated for several minutes in an anechoic chamber), experiences it when put in a sufficiently quiet environment.

Consequently, the model postulates that the processing of tinnitus-related neuronal activity within other than auditory parts of the nervous system, is dominant for clinically-relevant tinnitus. Specifically, the limbic and autonomic nervous systems are indicated as playing crucial roles.

Analysis of the problems reported by tinnitus patients, who exhibit a strong emotional reaction to its presence, a high level of anxiety, and a number of psychosomatic problems, indicated the limbic and autonomic nervous systems as crucial in clinically-relevant tinnitus cases. We postulated that the sustained activation of the limbic and autonomic nervous system is important in creating distress and, therefore, clinically-relevant tinnitus.

The tinnitus-related neuronal activity is processed by other parts of the CNS as well, including areas involved in memory and attention. It is possible to distinguish several feedback loops, with two major categories: loops involving the conscious perception of tinnitus and those that act at a sub-conscious level, with the subconscious loop dominant in the most patients. It is further suggested that the activation of the limbic and autonomic nervous systems by tinnitus-related neuronal activity follows the principle of conditioned reflexes.

The processing of tinnitus-related neuronal activity occurs in a dynamic balance scenario, with

continuous modification of the weights of synaptic connections. A continuous presence of tinnitus, combined with attention given to it, results in plastic modifications of synaptic connections, yielding the modification of receptive fields corresponding to the tinnitus signal, and enhancement of this signal. While the initial signal provided by the auditory system is needed to start the cascade of events, its strength is irrelevant, as the extent of activation of the limbic and autonomic nervous systems depends upon the strength of negative associations linked to tinnitus and the susceptibility of the feedback loops to be modified. It appears that the tinnitus-related neuronal activity may result from compensatory processes, which occur within the cochlea and the auditory pathways to minor dysfunction at the periphery.

Notably, once plastic modifications of neuronal connection occur, the peripheral signal itself may become of little importance, similarly as is observed in chronic pain. Indeed, there are clear similarities between tinnitus and chronic pain, including the phenomenon of prolonged exacerbation of tinnitus, as a result of exposure to sound, which is observed in some patients.

Enhancement of the sensitivity of single neurons within the auditory pathways may contribute to both tinnitus and hyperacusis, and could be responsible for the high (up to 40%) prevalence of hyperacusis in the population of patients with clinically-relevant tinnitus. Several peripheral and central mechanisms may be involved in hyperacusis. Furthermore, it is crucial to differentiate between hyperacusis and phonophobia, which results from

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different mechanisms and require different treatments. Hyperacusis and phonophobia both activate the limbic and autonomic nervous systems, but with different mechanisms than tinnitus. Once established, reactions of these systems are controlled by the conditioned reflex principle as in the case of tinnitus, but they are triggered by external sounds rather than tinnitus-related neuronal activity.

Based on the model, it is possible to suggest a treatment for tinnitus by interfering with tinnitus-related neuronal activity above its source and preventing it from activating the limbic and autonomic nervous systems (achieving habituation of reactions) and cortical area responsible for the awareness of tinnitus (habituation of perception). This approach is labeled Tinnitus Habituation Therapy (THT).

The neurophysiological model of tinnitus has been described and discussed in a number of publications, starting from the original paper in 1990 [1] and a recent update published last year [2–4]. The goal of this paper is to reiterate the main points of the model, with the emphasis on basic established neuroscience knowledge and principles applied to the field of tinnitus, and not sufficiently appreciated by the people who are not system neuroscientists.

From the first description of the model, the principles of the functioning of the nervous system, on which the model was based, were well known, strongly established, and considered to be a “handbook knowledge.” The neurophysiological model utilizes these principles in an innovative manner rather than work on hypothetical assumptions.

In contrast to previously proposed models which focus on individual systems, the neurophysiological model includes several systems of the brain involved in analysis of clinically-relevant tinnitus (i.e., tinnitus which creates discomfort, annoyance and requires intervention). All levels of the auditory pathways, starting from the cochlea, through all the subcortical centers and ending at the auditory cortex, are essential in creating the perception of tinnitus. When subjects are not bothered or annoyed by tinnitus, auditory pathways are the only pathways involved, and tinnitus-related neuronal activity is constrained within the auditory system. Therefore, although subjects are perceiving tinnitus, they are not disturbed by it.

In about 25% of people with tinnitus, strong negative emotions are induced, simultaneously with a variety of defensive responses of the body. The limbic and autonomic nervous systems then play a crucial role, and improper activation of these systems by tinnitus-related neuronal activity results in the problems described by patients.

The limbic system consists of a number of brain structures at or near the edge (limbus) of the medial wall of the cerebral hemisphere and include the following cortical structures: the olfactory cortex, hippocampal formation, cingulate gyrus, and subcallosal gyrus; as well as the following subcortical regions: the amygdala, septum, hypothalamus, epithalamus (habenula), anterior thalamic nuclei, and parts of basal ganglia. The limbic system exerts an

important influence upon the endocrine and autonomic motor systems. It influences directly the neuroendocrine and autonomic systems and controls multifaceted behavior, including emotional expression, seizure activity, memory storage and recall and the motivational and mood states [5]. Activation of various parts of the limbic system results in a spectrum of emotional states, including fear. This system is crucial in learning and development of conditioned reflexes.

The autonomic nervous system, one of the two main divisions of the nervous system, provides the motor innervation of smooth muscle, cardiac muscle and gland cells. It controls the action of the glands; the functions of the respiratory, circulatory, digestive and urogenital systems; and the involuntary muscles in these systems and in the skin. It assures homeostasis of the brain and body functions, controlling blood pressure, heart rhythm, muscle tension and hormonal release. The system also has a reciprocal effect on internal secretions, being controlled to some degree by hormones and exercising some control on hormone production. The autonomic nervous system consists of two physiologically and anatomically distinct, mutually antagonistic components: the sympathetic, and parasympathetic. The sympathetic division stimulates the heart, dilates the bronchi, contracts the arteries, inhibits the digestive system and prepares the organism for physical action. The parasympathetic division has the opposite effect. It prepares the organism for feeding, digestion and rest [6]. The activation of the sympathetic part is preparing the organism for action, while the activation of the parasympathetic system results in a relaxed, calm, passive state. Both systems are significant for our normal function and, among other things, are highly activated in a stressful situation and induce the “flight or fight” response. The connections between the auditory, limbic and autonomic systems with various cortical areas, as proposed in the neurophysiological model of tinnitus, are outlined in Figure 1.

The model, illustrates that the sustained activation of the limbic and autonomic nervous systems is responsible for the distress induced by tinnitus, consequently, for clinically-relevant tinnitus. Activation of both systems can be achieved through two routes. One includes stimulation of autonomic and

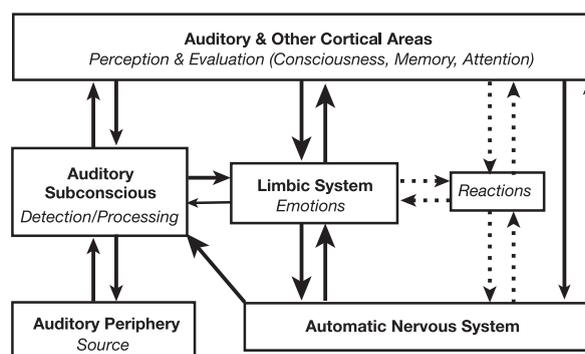


Figure 1 The neurophysiological model of tinnitus.

limbic systems from higher level cortical areas, which are involved in our awareness, verbalization and beliefs. The other one, subconscious, provides stimulation from the lower level auditory centers. The activation going through these two routes changes during the process of development of tinnitus as a clinical problem.

In the vast majority of cases, tinnitus-related neuronal activity within the auditory pathways cannot be linked to any pathology. It could be explained by the compensatory action occurring within the auditory pathways to dysfunction occurring within the cochlear or the peripheral level of the auditory system. Notably, the experiment of Heller and Bergman, showed that the perception of tinnitus cannot be pathological, since essentially all of their subjects (94%) experienced tinnitus when placed in an anechoic chamber [7].

At the same time, for a significant part of the population of tinnitus patients, the physiological or psychiatric evaluations are normal, before the emergence of tinnitus. Therefore, for the dominant majority of patients the auditory, limbic and autonomic nervous systems function correctly. Tinnitus as a problem arises from inappropriate activation of the limbic and autonomic nervous systems by the tinnitus-related neuronal activity, which originated in the auditory system.

Knowledge how conditioned reflexes are created is necessary to understand how the neutral signal of tinnitus can evoke persistent strong distress. Basically, to create a conditional reflex the temporal coincidence of sensory stimuli with negative (or positive) reinforcement is sufficient (Figure 2). This initial association can be totally coincidental, without any real dependence. These types of associations of sensory stimuli are created all the time in a normal life, and are the basis for many "superstitious reactions." For example, if a man wears a green tie when he has very unpleasant interaction with his boss, he will develop a feeling of discomfort every time he wears this specific tie. Due to the generalization principle, this will affect other green ties as well.

However, as long as the sensory stimulus is limited in time and there is no functional dependence of

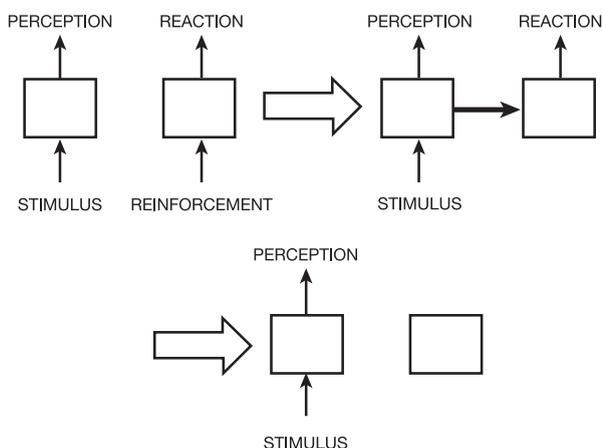


Figure 2 The principles of establishing conditioned reflex

the stimulus, this conditioned reaction will gradually disappear (habituate) due to passive extinction of the reflex (the sensory stimulus is present, but is not accompanied by a reinforcement – Figure 2). Since the 1930's habituation has been defined as "The extinction of a conditioned reflex by repetition of the conditioned stimulus, it is the method by which the nervous system reduces or inhibits responsiveness during repeated stimulation" [8,9]. Habituation of perception of this stimulus will follow in the same manner as for all unimportant stimuli.

Understanding the principles governing habituation of reaction to a stimulus, and habituation of its perception, is another important point. Habituation of reaction, is defined as "disappearance of a reaction to a neutral stimulus due to its repetitive appearance without reinforcement." Habituation of perception occurs when awareness of this particular stimulus disappears. Habituation of reaction and perception is a natural process. It is a crucial characteristic of brain function necessary due to our inability to perform two tasks requiring our full attention at the same time. If forced to monitor all of the incoming sensory stimuli, we would not be able to perform any task, except switching our perception from one sensory stimulus to the other, and we would become basically paralyzed in our actions.

To solve this problem, the central nervous system screens and categorizes all stimuli at the subconscious level. If the stimulus is new and unknown, it is passed to a higher cortical level, where it is perceived and evaluated. However, in the case of a stimulus to which we have previously been exposed, the stimulus is compared with patterns stored in memory. If the stimulus was classified as non-important and does not require action, it is blocked at the subconscious level of the auditory pathways, does not produce any reactions or reach the level of awareness. The reaction to this stimulus and its perception is habituated. In everyday life, habituation occurs to the majority of surrounding us sensory stimuli.

However, if a specific stimulus was classified as important, and, on the basis of comparison with the patterns stored in memory, it was linked to something unpleasant or dangerous, this stimulus is per-

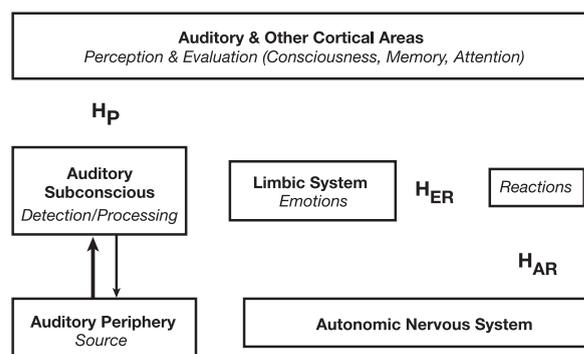


Figure 3 Habituation of autonomic (H_{AR}) and emotional (H_{ER}) responses

ceived and attracts attention. Furthermore, the autonomic nervous system is activated, inducing reaction to this stimulus (frequently of the “fight or flight” category) and reinforces memory patterns associated with this stimulus. Consequently, if the previous assessment of the importance of a stimulus has been confirmed, this specific stimulus becomes even more important and its next appearance will result in faster identification, even in the presence of other competing stimuli, and the habituation of this stimulus will be blocked. In the case of auditory stimuli, our auditory system becomes tuned into recognizing specific patterns of sound which have negative links. All of these processes are occurring at the subconscious level without resulting in the perception of a sound. As a side effect of this, since attention is attracted and forced to this particular stimulus, attention is detracted from any other tasks.

The situation for tinnitus is identical for the initial stage of development of conditioned reflex, with tinnitus as a sensory signal, and the activation of the sympathetic autonomic nervous system as reaction. At the initial stage of the emergence of tinnitus as a problem, the perception of tinnitus is associated with something negative. A person may or may not be aware of the presence of tinnitus before this point of time. This negative association can occur due to the random coincidence of the perception of tinnitus and a feeling of discomfort or stress, by new negative information about tinnitus, or by a rapid, transient increase of tinnitus loudness. As in the case of any external stimuli, it is sufficient that a person perceives tinnitus, while being under a higher level of negative activation of the autonomic nervous system, resulting in feeling of distress or discomfort, which is not due to tinnitus at all. Indeed, for the majority of tinnitus cases, the emergence of tinnitus is associated with something not related to the auditory system, such as retirement, death in family, divorce, work problems, etc.

Negative reinforcement can be provided by false information about tinnitus provided by a friend, colleague, a family member, or unfortunately, frequently by a health professional. This is known as negative counseling and indeed, for a number of patients, this is why they developed clinically-significant tinnitus. After checking with a health professional and learning that “nothing can be done, you will have to live with it the rest of your life and we better check you for a brain tumor.” This negative counseling provides very strong negative reinforcement, establishing the conditioned reflex between tinnitus and reactions of the autonomic nervous system.

Another scenario of developing this conditioned reflex occurs when there is rapid development of tinnitus perception or an increase in its intensity. The patient might be concerned about an unknown new signal, which could indicate to him that something wrong is happening within his head or he could simply be annoyed by the continuous presence of a sound over which he has no control (similarly, as he would be annoyed by a continuous

external sound). The emergence or increase of tinnitus intensity can be totally accidental and transient, and if not for the self-sustained reinforcement occurring for tinnitus, it would undergo habituation as an external unimportant stimulus.

There is a distinctive difference between the coincidental reflexes to external stimuli and tinnitus. Tinnitus is typically continuous or lasting for hours or days. This makes dissociation of tinnitus with negative reaction more difficult. Still, extinction of this conditioned reflex could happen, if not for the second feature of this particular situation. The negative reinforcement is self sustained (Figure 1). Once tinnitus is labeled as something negative, potentially indicating danger or an unpleasant situation, a cascade of events is started. The continuous presence of tinnitus will induce prolonged activation of the autonomic nervous system, which cause distress at the behavioral level. The distress will serve as the negative reinforcement, further enhancing the strength of this conditioned reflex (Figure 1). Note, that this sub-loop is working within the autonomic nervous system without need for additional enhancement from other systems, which are contributing as well to further strengthening of this reflex. Consequently, self enhancing conditioned reflex is created, which will increase the strength of reactions to the limit determined by parameters characterizing the systems involved, and plasticity of their connections.

Under such conditions, the natural habituation of the tinnitus signal becomes impossible. In everyday life, this results in people having problems with their work, concentration and sleep. The simplistic description of the above process can be outlined to a patient as increased concern to tinnitus resulting in an increase of its significance, which increases the amount of time a person pays attention to it. This is a classical feedback loop or the “vicious” circle scenario, which causes the patient to increase the level of his distress up to the level of mental and physical endurance. At this stage, the patient will move from acute tinnitus, which can be easily relieved by TRT counseling or cognitive behavioral therapy, into a chronic stage, which is much more difficult to deal with than the earlier stage.

Once patients reach high levels of stress, annoyance and anxiety, tinnitus become the dominant factor in their lives and interfere with everyday activities, including sleep. Sleep deprivation in itself creates profound changes in a patient’s behavior (i.e., mood swings, problems with attention, inability to logically analyze a situation, a tendency to depression), which are very frequently seen in tinnitus patients.

When patients reach a high level of activation of the autonomic nervous system, another mechanism is activated. This natural mechanism, which under normal conditions is very valuable, when improperly switched on in tinnitus and hyperacusis patients, has a devastating effect on the quality of their life. It is known as a contradictory action of drives or motivations and is one of the defense mechanisms in our body. When a person is under

heavy stress and anxiety, the “fight or flight” reaction is activated and the body prepares for defensive or offensive actions. A high level of activation of the defensive mechanisms results in the suppression of all emotions related to relaxation and pleasure. This mechanism is well recognized in psychology and animal neuroscience and is actually used in the animal model for tinnitus [10], as the model utilizes the Pavlovian suppression, as introduced by Estes and Skinner in 1941 [11]. In this technique, fear conditioned in animals results in their decreased ongoing drinking or eating. By evaluating the decreases in ongoing drinking or eating, it is possible to measure their extent of fear.

In the case of tinnitus, high levels of stress and anxiety suppress the patients’ abilities to enjoy previously liked activities. This is reflected in frequent descriptions by patients that they are just going through the motions of activities in their lives and interactions with their families because it is expected of them or it is part of their routine, and that they have lost the ability to enjoy these activities. When patients lose the ability to enjoy their lives, the consequence is falling into a depression, which is observed in the majority of tinnitus patients. Frequently, patients are reluctant to disclose this issue, but once they understand the neurophysiological basis of this problem, it has a positive clinical impact on their recovery.

The conditioned reflex link tinnitus signals with reactions of the limbic and autonomic nervous systems at subconscious levels. Thus, the presence of tinnitus-related neuronal activity directly activates the limbic and autonomic systems, without the need or necessity of going through the high cortical areas involved in conscious thinking about tinnitus, verbalization, beliefs, etc. (Figure 1).

How is extinction induced in this conditioned reflex? It is well recognized that conditioned reflexes of any kind cannot be altered simply by changing a person’s belief or opinions about the situation. It would be impossible, for example, to change our driving habits from driving on the left-hand side of the road to the right side by just telling ourselves, “well, all the rules are symmetrical and the car coming on the right side of us is not indicating any type of problem.”

Another interesting consequence is that a decrease in the strength of the stimulus (tinnitus) alone will not be particularly effective, as the strength of a conditioned reflex is primarily determined by the reinforcement, and is secondary to the intensity of stimulus.

Although it is impossible to change some reflexes by simply changing a belief, each reflex can be retrained, modified or reversed by proper training. Two main categories of training can be distinguished. Under one condition, named “passive extinction,” a stimulus is repeated, but reinforcement is no longer given. An example is driving a car while cars are passing us on the right side of the road, but nothing bad happens. This approach has been discussed already, and it is main technique to be applied to tinnitus. In the other retraining

technique, “active extinction,” occurs when the presence of the same stimulus is reinforced in a manner totally opposite to the previous condition (e.g., positive in place of a negative). Active extinction is more difficult to apply in the case of tinnitus, but in some patients it is possible to associate tinnitus with something positive in their life which they did not realize existed.

In the case of tinnitus, it is impossible to remove the reactions induced by the excitation of the sympathetic autonomic nervous system or even change them in a substantial manner. The solution to achieve the passive extinction of conditioned reflex in which both stimulus (tinnitus) and negative reinforcement are continuously present, is to decrease the magnitude of this negative reinforcement over a period of time. This will result in partial weakening of the reflex and has to be applied consistently to yield positive effects. Moreover, it is fundamental that patients understand these principles so that the enhancement of this reflex by including too much of verbal thinking and beliefs can be minimalized.

Activation of the autonomic nervous system results from the combined action of the lower subconscious loop and the upper loop, which involves the highest levels of the cortical areas. In the first step, we are attempting to decrease activation from the cortical area by convincing the patient about the benign nature of tinnitus, and by presenting tinnitus as a result and side effect of a positive, helpful, compensatory activity occurring within the auditory system (Figure 1). More detailed description is presented in the accompanying papers [12,13].

Once activation of the autonomic nervous system is lowered, this decreases negative reinforcement to a signal that is continuously present and decreases the strength of the conditioned reflex. This causes further decreases in the reaction. Once tinnitus have achieved a neutral status, its habituation is inevitable, as the brain is continuously habituating to all types of old and new stimuli, assuming they are not significant.

The interaction between these centers occurs in a dynamic-balanced scenario (i.e., neuronal connections linking those centers are undergoing continuous modification), depending upon the strength of ongoing stimulation and connections among all systems involved and in the central nervous system. For example, exactly the same stimulus can be perceived quite differently, if a subject is under a very high level of stress and anxiety induced by any factor. To modify connections within such a network, it is necessary to act in a consistent and continuous manner, as otherwise weakened, but present conditioned reflex will enhance itself following principles outlined above.

In addition to decreasing the strength of the activation of the limbic and autonomic nervous systems, the second component of TRT is sound therapy. It is based on a feature of the central nervous system that all our senses are working on the principle of differences of the stimuli from the background and are not linked directly to the physical

strength of a stimulus. At this moment we cannot easily suppress tinnitus-related neuronal activity, but by increasing background neuronal activity, we are effectively decreasing the strength of this signal activating the limbic and autonomic nervous systems and being processed in all the centers involved. There is no simple proportional relationship between the differences in tinnitus and background neuronal activity and induced by it reactions. Nevertheless, we can achieve a decrease of reactions induced by tinnitus, and through this facilitate extinction of the conditioned reflex.

The use of sound, but not of anyone particular device is so crucial to TRT that it can be labeled Habituation Sound Therapy (HST), with the double meaning of the use of sound and habituation perception of tinnitus as a sound. The issue of sound therapy is discussed in an accompanying paper [14]. One aspect, related to the use of close to threshold sound levels, deserves mentioning as it results from a recent finding in neuroscience of the importance of stochastic resonance. This term describes a phenomenon of the decreased threshold of detection of weak signals in nonlinear systems (such as cochlea or any part of the brain), by adding weak noise and of the enhancement of weak signals by adding low levels of noise. It has been demonstrated to exist in a number of systems. In the past, it was debated if it could act in a high frequency and intensity range to play a significant role in the auditory system. Recent findings documented that it acts to at least 4 kHz, and plays a role in transduction occurring in hair cells utilizing the Brownian motion to enhance detection of the signal [15]. It also has been documented in the auditory nerve [16], and was proposed to be used in the case of cochlear implants [17].

Stochastic resonance has a profound implication on the use of sound in TRT, suggesting that the use of low, close to threshold sound levels can be detrimental and rather than promoting it, can slow down the habituation of tinnitus. Indeed, results obtained with the use of different sound levels in TRT fully support this postulate [18], and are in agreement with observation from our early patients, who were advised about use of sound at the level close to threshold.

Another recent finding in the neurosciences has implication on how we are treating tinnitus patients with unilateral deafness or unilateral profound hearing loss. It is common knowledge that the nervous system exhibits an enormous amount of plasticity and that information from various sensory systems is integrated into a coherent entity. The visual and vestibular systems are classical examples of such a collaboration. It also has been recognized that, in the absence of sensory input, phantom perception occurs (phantom limb, phantom pain, tinnitus), with accompanied reorganization of receptive fields.

A few years ago a new dramatic development was reported for controlling phantom pain and phantom limb by utilizing multisensory interaction [19]. Phantom pain and phantom limb frequently cannot be controlled by any pharmacological or

surgical approach. However, by introducing visual input, it turned out to be possible to control phantom pain in patients with one of their hands amputated. These patients were instructed to put the healthy hand into the box with a glass top and the mirror inside, so they saw only the healthy hand and its mirror reflection, which mimicked the missing hand, and to move the hand. After several sessions the phantom pain, which could not be controlled by other means, disappeared. Presumed mechanisms of action involved reorganization of receptive fields of somatosensory representation of the hands by visual input and partially restoring the balance disturbed by the lack of sensory input from the missing hand. Recent data with fMRI strongly supported this postulate [20].

This information had direct effect on the treatment of tinnitus in patients with profound unilateral hearing loss or unilateral deafness. While the high level of plasticity of the nervous system had been recognized long ago, the extent of plasticity and reorganization of receptive fields within the auditory system was not sufficiently appreciated. Recent data changed this situation dramatically with results showing reorganization of the tonotopic cortical maps due to the presence of tinnitus [21]. Based on results with phantom pain, the idea was to utilize the combined actions of the auditory and visual systems by fitting patients with CROS, BICROS or transcranial systems. This provided them with auditory information from a whole auditory space, which in combination with the information, from the visual system which should restore spacial localization of the sound and modify receptive fields in the auditory pathways. The clinical results confirmed that these patients had partially restored their space localization of auditory stimuli (tested with closed eyes). Furthermore, as hoped, this method also was helpful for their tinnitus. A systematic study on a large number of cases is needed, but results obtained so far are very encouraging.

In summary, a deep knowledge of neuroscience could be advantageous in working on better understanding of the mechanisms of tinnitus, and in proposing and shaping new methods of treatment aimed at its control. Due to space limitations, the issues related to hyperacusis were not discussed here, but similar principles apply. As neuroscience is rapidly developing, it is important to monitor the new developments, and to test the relevant findings in experimental and clinical settings, to provide increased understanding of tinnitus and thereby improving care for tinnitus and hyperacusis patients.

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Delineating tinnitus-related activity in the nervous system: Application of functional imaging at the *fin de siècle*

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As the “*decade of the brain*” comes to an end, we become the beneficiaries of those accomplishments that neuroscience research has made over this time period. One domain that has shown explosive growth, coupled with impressive advancements, is functional neuroimaging using methods such as positron emission tomography (PET) and functional magnetic resonance imaging (*fMRI*). In a relatively short period of time, this area of investigation has advanced our understanding of the neuroanatomical and neurophysiological substrate of sensory, motor, and linguistic information processing in the human nervous system *in vivo*, and has provided details on connectivity patterns and interactions within distributed neuro and neuro/cognitive networks. Studying phantom perceptions and/or internally generally perceptual experiences like tinnitus, hallucinations, pain, synesthesias, imagery, etc. has only begun to be explored by these powerful imaging modalities. Whereas these later clinical entities pose significant challenges for researchers in this area, evidence is accumulating which suggests that tinnitus-related neural activity is capable of being studied with available technology.

Thus, as we rapidly approach the beginning of the 21st century, a new frontier for auditory neuroscience has opened for exploration. In addition to determining loci of tinnitus related activity, both PET and MRI are capable of providing *in-vivo* biochemical information, which can compliment existing paradigms. In fact, one of the greatest potential strengths of PET for example, is the ability to measure neurotransmitters and their receptors within the brain in nanomolar proportions. By incorporating a variety of imaging methods into the study of tinnitus related activity, one has the potential to validate and/or expand upon existing animal and human models, distinguish different groups of individuals and aid in delineating and monitoring various treatment options.

Thus, based on available information, it is reasonable to suggest that a variety of functional neuroimaging modalities are poised to play an important role in tinnitus research in the new millenium. We therefore approach the 21st century with guarded optimism that advancements already achieved will serve as the momentum to carry us to a new level of understanding. The available knowledge obtained to date will set the stage and provide the foundation for future advancements.

Introduction

The lack of objective, non-invasive methods for detecting and localizing tinnitus-related neural activity in the nervous systems in humans, is one of many reasons that have limited advances in this area of auditory research. The study of phantom perceptions like tinnitus and other perceptual experiences, which occur in the absence of overt sensory stimulation [i.e., hallucinations (auditory and visual), pain, synesthesias, and mental imagery, are just begin-

ning to be explored with contemporary neuroimaging modalities. Whereas it is an optimistic expectation, it is nevertheless a realizable goal, that the same advancements made in understanding human information processing in sensory, motor and cognitive/linguistic systems *in vivo* to external stimulation, can occur in the study of phantom perceptions like tinnitus. Herein, we focus on ways in which contemporary functional imaging modalities have been used to study tinnitus related neural activity at the end of the 20th century. It is this pioneering work that will lay the foundation for future advancements.

From an historical perspective, changes in brain circulation related to mental activity has been reported for over a century based on different technologies available at the time of investigation [1, for

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a review]. However, it was only with the advent and application of positron emission tomography (PET) in the 1970's, that *in vivo* functional imaging experiments on humans became possible [2,3]. Using radioactively labeled probes injected into the body, PET measurements reveal that changes in blood flow and glucose metabolism far exceed that of oxygen metabolism during brain activation [4,5], leading to increased arteriovenous oxygenation levels. Combined with the observation which relates the oxygenation level of hemoglobin (Hb) to local magnetic field perturbations [6], has led to the imaging of blood oxygen level dependent (BOLD) changes, initially reported in laboratory rats using MRI [7]. Subsequent studies using MR techniques have further demonstrated the viability of BOLD contrast in functional activation studies in human brains [8,9]. In comparison to BOLD methods, external susceptibility agents in the form of a bolus injection have also been used in sensory (visual) activation studies utilizing MRI [10]. Nevertheless, the intrinsic contrast provided by the paramagnetic deoxyhemoglobin of blood is preferred over the injection of external susceptibility agents, primarily because the rapid passage of the contrast agent through the brain imposes substantial restrictions on paradigm designs (i.e., duration and number of repetitive on/off cycles, etc.). It is becoming well accepted that blood acts just like a T2 altering relaxation agent with the degree of paramagnetism determined by its oxygenation state pursuant activation [11]. Furthermore, with MRI, blood flow also serves as a T1 modulation mechanism due to the exchange of H₂O across the blood brain barrier (BBB) during traversal through the capillaries [12,13].

Conceptually, both PET and *fMRI* attempt to spatially localize synaptic activity in response to a stimulus by using techniques that are sensitive to external manifestations of neuronal changes. Functional MRI studies begin with a localizer image, where a standard MRI acquisition is performed to preselect slices of interest to be used during imaging applications. In both PET and *fMRI*, functional acquisitions are then conducted in the presence of an external intermittent stimulus. In most paradigms that evaluate sensory and motor systems, "activation/on" states, which represent stimulus presentation, are alternately interleaved with "rest/off" states, where no stimulus is presented. Upon completion of the stimulus presentation and acquisition process, the functional data are registered to compensate for in-plane head motion. Subsequently, statistical tests are conducted to determine whether the data collected during the "activation/on" state are significantly different from those collected during the "rest/off" state. Results of statistical testing are then thresholded, color-coded, and co-registered onto the anatomical reference images or to another anatomical coordinate system (e.g., Talairach) to allow for interpretation and display. Thus, the ultimate goal of any functional study is to identify the brain parenchymal contribution where neuronal activity resides. In *fMRI* in particular, it is

the capillaries and their surrounding gradients that are of primary importance. The technical issues which surround this complex area, while beyond the scope of the present paper, are reviewed in detail elsewhere [14].

In the study of human neuro-function, *fMRI* is particularly advantageous because it is completely non-invasive, does not require exposure to ionizing radiation or radiopharmaceuticals, has good temporal and spatial resolution, is well suited for single-subject repeated-measurement designs, and the results can be superimposed on the individual's own brain structure (MRI) without the need for complex image transformation or warping [15,16,17,18]. At present, the main disadvantage of *fMRI* for auditory studies relate to imager/system related background noise. Imager/system noise is a complex issue because of level effects and sound/vibration transmission routes (air and bone conduction). As a result, passive attenuation devices (e.g., insert earplugs, headphones, etc.) can only be partially successful at noise reduction [see 19,20, for a discussion of relevant issues]. However, advancements in this area are being made. Additionally, besides passive attenuation or even active noise cancellation devices, other options include restricting the number of slices studied and choice of pulse sequence [21,22,23]. Whereas the temporal and spatial resolution of PET is poorer than *fMRI*, currently it is advantageous for use during auditory studies because far less background noise is generated during data acquisition.

Imaging tinnitus-related activity

Because tinnitus is often perceived as a constant sound in the absence of external acoustic stimulation, it is reasonable to ask the question, "how is it possible to image tinnitus-related neural activity?". The novel idea that tinnitus could be imaged was initially proposed by Sasaki *et al.* [24], based on an animal model using autoradiography and a glucose tracer, [¹⁴C]2-deoxyglucose. At present, several approaches to this topic have been explored with relative degrees of success. These include:

- (1) Evaluation of glucose metabolism in patients with constant chronic tinnitus, using PET [25,26];
- (2) Evaluation of individuals that can *modify/modulate* a constant background tinnitus by performing some type of overt behavior in another sensory, motor or sensory-motor modality i.e., *jaw clenching, eye gaze*, using PET [27,28];
- (3) Evaluation of individuals that can *activate/trigger* their tinnitus (turn it on and off) by performing an overt behavior in another sensory, motor or sensory-motor modality, i.e., *static or dynamic change in eye position* from a neutral head-referenced condition or cutaneous stimulation of the hand or finger tip region, using PET and *fMRI* [29,30,31,32];
- (4) Evaluation of stimulus induced modification of lateralized tinnitus activity, using *fMRI* [33];

- (5) Evaluation of pharmacological induced modification of tinnitus related neural activity, using PET [34].

Evaluation of glucose metabolism in patients with constant tinnitus

The assumption that increased metabolic activity following deafferentation of the auditory periphery could be related to the tinnitus percept, was initially reported by Sasaki, Kauer, Babitz [24] based on autoradiography experiments. Positron emission tomography is analogous to *in vivo* autoradiography, as such, metabolic aspects of signal processing, both endogenously and/or exogenously generated, may be evaluated with this technique. Along these lines, Arnold et al [25] studied adult patients with chronic tinnitus and hearing loss using PET and [¹⁸F] deoxyglucose probes and compared them to controls without tinnitus or hearing loss. They assumed that if tinnitus were associated with synaptic hyperactivity, then such activity would be reflected by an increased glucose metabolism, measurable by PET. In individuals with tinnitus but not in controls, asymmetric metabolic hyperactivity (predominantly localized to the left hemisphere) was detected in the region of Heschl's gyrus in the *primary* auditory cortex. Additional work in this area has also been carried out by Oestreicher *et al.* [26]. In this study, individuals with bilateral and unilateral tinnitus (14 right, 6 left) were studied with a similar FDG probe. Increased glucose metabolism was found in primary auditory cortex (left > right side). Decreased activity was observed in insulo-opercular area on the left and in the insula region on the right. Clusters of decreased activity were also noted in occipital-parietal cortex bilaterally. In individuals with "*unilateral deafness*", only slight increases were noted in primary auditory cortex. Bilateral decreases were also observed in the insular region and parietal cortices. Thus, changes in glucose metabolism were observed in *primary* auditory cortex and other regions in the central nervous system.

Evaluation of individuals that can modify a constant background tinnitus by performing some type of overt behavior in another sensory, motor or sensory-motor modality

In addition to studying glucose metabolism with PET, several other approaches have been proposed which would satisfy the conditions necessary for imaging tinnitus with *fMRI*. That is, if the tinnitus percept could somehow be consciously modulated (i.e., changed in loudness), or turned on and off, then the conditions necessary for assessing a difference image would be satisfied. It was suggested that individuals with gaze-evoked tinnitus could potentially meet these criteria, either by internally generating on and off states during data acquisition or

modulating an existing constant tinnitus [35]. We emphasize here a distinction made previously between the pure form of this condition and a variant form in which the tinnitus perception is modified in some way. In the pure form of gaze-evoked tinnitus, tinnitus is completely absent in a particular setting (a central eye-gaze location), and present only when a change in the spatial position (left/right horizontal; up/down vertical) of eye gaze is maintained from a neutral head-referenced position [36,37]. This is in contrast to a variant form of this condition where change in eye gaze just serves to modulate a constant background tinnitus. In retrospect, this may turn out to be an important distinction, since different activation sites may emerge during imaging and different mechanisms may be involved in these two different conditions.

In addition to eye gaze, tinnitus loudness can also be modulated in some individuals by performing oral-facial movements (jaw clenching). Lockwood *et al.* [27] were first to document and localize several brain activation sites in this select group of individuals. Lockwood *et al.* [27] used PET and a between subjects design to evaluate (1) if neural activity underlying changes in tinnitus loudness produced by oral facial movements could be detected, and (2) whether changes in auditory system organization, secondary to high frequency cochlear hearing, could also be evaluated with this methodology. Two groups were scanned separately during OFMs (tinnitus group), jaw clenching (normal control group without tinnitus or hearing loss), during unilateral 500 Hz and 2000 Hz tone burst stimulation, and at rest (no activity). Normal controls showed bilateral activation of sensory-motor cortex and supplemental motor area in response to jaw clenching. In two patients where OFMs *increased* tinnitus loudness (i.e., where tinnitus was localized to right ear in one patient and in the left ear in the other), increases in CBF were observed in sensory-motor cortex, primary auditory cortex in the left superior temporal gyrus and in a region near the medial geniculate nuclei (MGN). To separate changes in CBF due to increases in tinnitus loudness, group subtractions were performed between PET results obtained during jaw clenching in controls and OFM in tinnitus patients. The subtraction procedure showed residual activation in the left thalamic region (left MGN) in the tinnitus group. This was interpreted as indicating that the post subtraction increase in neural activity was due to the increase in tinnitus loudness. In two patients where OFMs *decreased* tinnitus loudness (i.e., where tinnitus was localized to right ear in both individuals), a decrease in CBF was observed in the posterior and mid portion of the left middle temporal gyrus. Here the subtraction procedure showed a region of reduced CBF in the temporal lobe and hippocampus of the left hemisphere. Acoustic stimulation in the right ear of both patients and controls produced bilateral activations of the transverse temporal gyri and adjacent portions of the superior temporal gyri. However, in patients and not controls, activation was also seen in the left

hippocampus for the 2000 Hz condition only. Group subtraction for the 2000 Hz condition showed excess activation in patients in the primary auditory cortex, anterior left temporal lobe and insula but *not* in hippocampus or lenticular nuclei.

Lockwood *et al.* [28], also reported on a group of individuals that could modulate (increase) the pitch and loudness of a constant tinnitus with sustained lateral gaze (gaze-evoked tinnitus). Six of seven had profound hearing loss on the involved side, varying degrees of facial nerve injury, and mild abnormalities of ocular motility. Single subject repeated measures analysis produced significant results in all individuals but substantial variations among individuals were also noted. Activation sites reported by these investigators included areas of brainstem (left vestibular nucleus), and primary auditory or auditory association cortices. Additionally, after averaging data between subjects and normalization to Talairach coordinates, activation foci were also noted in supramarginal gyrus and cerebellar vermis.

Evaluation of individuals that can activate their tinnitus (turn it on and off) by performing an overt behavior in another sensory, motor or sensory-motor modality

Cacace *et al.* [29,30] reported activation sites associated with individuals with gaze-evoked tinnitus using *fMRI*. The initial report noted activation in the upper brainstem and later studies showed lateralized activation in posterior lateral areas of auditory cortex. Not all individuals studied have been successfully imaged, however. In those cases where useful data could not be obtained, it was always associated with excessive head movement artifacts during data acquisition secondary to anxiety/nervousness during task execution within the closed environment of the MRI scanner [see 32, case 1]. In these instances, attempts at image reregistration, using a variety of methods, have not been successful.

Giraud *et al.* [31] used PET to study a group of individuals with gaze-evoked tinnitus which was manifest after resection of large acoustic neuromas. Each individual had profound unilateral hearing loss, and described a loud auditory sensation following eye movements in the horizontal plane. These investigators found bilateral increases in cerebral blood flow, associated with gaze-evoked tinnitus activation typically higher in the left versus right temporal-parietal areas (i.e., in auditory association areas). These data suggest that activation of *primary* auditory regions is not necessary for the perception of tinnitus.

In two individuals, cutaneous-evoked tinnitus followed neurosurgery for space-occupying lesions of the skull base or posterior craniofossa, where hearing and vestibular function were lost completely and acutely in one ear and facial nerve paralysis was present either immediately following surgery or occurred as a delayed onset event. In this previously

unrecognized phenomenon, tinnitus was triggered by direct stimulation of the upper hand or fingertip region. When a finger opposition tapping task was used to trigger the tinnitus percept during *fMRI*, localized activation was observed in the temporal-parietal junction [32]. This represented activation in auditory centers of the brain on the superior aspect of the temporal and inferior aspect of the parietal lobes. The finger opposition tapping task which elicited the tinnitus, also produced activity in the right (ipsilateral) caudate area, slight activation in the contralateral orbital frontal region and prominent activation in the contralateral motor, premotor and pre-Rolandic sulcus regions. A control finger opposition-tapping task with the other hand produced activation limited to the contralateral motor cortex, premotor cortex and pre-Rolandic sulcus regions. These data dissociated cutaneous-evoked tinnitus-related activity from activation produced by the finger opposition tapping task using the opposite hand.

Evaluation of stimulus induced modification of tinnitus related neural activity

Levine *et al.* [33] has suggested an approach to assessing individuals with lateralized constant tinnitus using acoustic stimulation/masking paradigm and the single slice *fMRI* method [38]. In a group of adults with normal hearing sensitivity and tinnitus lateralized to one ear, they found that presentation of binaural noise produced activation in the inferior colliculi that was always more asymmetric in individuals with lateralized tinnitus than in controls. Interestingly, in comparison to normal controls, all individuals with unilateral tinnitus had abnormally low *fMRI* activations in response to binaural noise in the inferior colliculus contralateral to the tinnitus percept.

Evaluation of pharmacological induced modification of tinnitus related neural activity

Other important paradigms have been reported in studying tinnitus-related activity in the CNS. For example, Mirz *et al.* [34] used PET in conditions of tinnitus suppression/inhibition using narrow band acoustic masking, pharmacological tinnitus reduction using intravenous lidocaine and in combined conditions of acoustic masking plus lidocaine administration. In this study, tinnitus related activity was localized to the middle and superior right prefrontal cortex and right posterior (middle temporal and precuneus) gyri. Deactivations were observed in the left transverse temporal gyri.

Like gaze-evoked and cutaneous-evoked tinnitus, synesthesia is a condition where stimulation in one modality can evoke a conscious perceptual experience in another modality (cross-modal phantom perception). For example, in color-word synesthesia, words can serve to activate specific colors in

the absence of visible-luminous stimuli. In a PET study of color-word synesthesia, Paulesu *et al.* [39] found that specific words but not tones evoked cross-modal synesthetic perceptions. Whereas words activated perisylvian language areas, non-primary visual association areas (posterior inferior temporal cortex and the parietal-occipital junctions) it was also found that prefrontal cortex, the insula, and superior temporal gyrus was also activated. Significantly, this study indicates that brain areas concerned with language and visual-feature integration may underlie these particular cross-modal synesthetic perceptions without requiring overt activation of the *primary* visual cortex. Additionally, other phantom perceptual experiences such as hallucinations or pain may also share common properties with tinnitus. At present, the limited number of functional imaging studies concerning these topics [see 14,41], do not allow us to reach a firm conclusions.

In summary and with respect to tinnitus localization studies, results from Lockwood *et al.* [27], Arnold *et al.* [25] and Giraud *et al.* [31] found a left hemisphere trend in localization or enhanced signal strength during change in tinnitus loudness. In some instances, these effects occurred regardless of where tinnitus was localized subjectively [25,27] and in other instances, enhanced signal strength occurred in the hemisphere contralateral to the ear (right side) with profound hearing loss [31]. Whereas Lockwood *et al.* [27] reported limbic system activations, Mirz *et al.* [34] reported activations in brain regions known to subservise attention, emotion and memory, and Oestreicher *et al.* [26] noted decreased activation in the insula region of the brain, neither Arnold *et al.* [25], Giraud *et al.* [31] nor Cacace *et al.* [29,30,32] found limbic system foci in individuals with chronic tinnitus or in those with gaze-evoked or cutaneous tinnitus. Limbic system linkage, if consistently found or on the other hand not consistently documented, could help to validate, expand, and/or redirect conceptualizations of existing models of tinnitus [40].

Based on available information at this very early stage of development, it appears reasonable to suggest that functional imaging is a promising research tool to objectively document and localize tinnitus related neural activity in humans. Furthermore, if it can be shown that these methods can delineate different patient populations and document treatment efficacy, then such technology has potential to evolve into the clinical arena. Since all major medical centers have MRI and relatively few have PET scanners, it would seem logical that developing tools based on MR technology would be most efficacious and cost efficient.

Conclusions

Although experimental in nature, and whereas many issues remain to be fully resolved, *fMRI* and *PET* are rapidly evolving into a variety of robust

procedures that have considerable potential and are poised to play an important role in tinnitus research. As the 20th century comes to an end, we approach the new millennium with guarded optimism that advancements accrued in neuroscience research will serve as the momentum to carry us to a new level of understanding of tinnitus-related neural activity in the nervous system. Tinnitus research has certainly been invigorated by innovative research designs using functional imaging. Whereas many challenges remain, they will be challenges for the next century to resolve.

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Quality of family life of people who report tinnitus

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The impact which tinnitus has on people's quality of life is important. In assessing the public health priority of tinnitus and indeed in assessing the benefit that accrues from intervention we should try to assess the impact that tinnitus has on people and on their family and those with whom they work. We have assessed the health related quality of life using the SF-36 Aspects of Health Questionnaire and the wider impact of tinnitus using a new Quality of Family life Questionnaire in two groups of patients – the first awaiting a specialist appointment (group A) and the second a group of people who have attended for a specialist appointment and been discharged (group B). We analysed the results using a recently developed outcome measure, the SF-6D. This measure is a preference-based single index derived from the SF-36 questionnaire. The SF-6D showed a statistically significant better scores for individuals who have been discharged in comparison to those who are on the waiting list, when controlling for other factors that might influence the SF-6D measure. Furthermore there were systematic differences between those on the waiting list and those who had been discharged with respect to aspects of Quality of family life, particularly in the areas of understanding tinnitus and allaying fears.

Introduction

Tinnitus is a chronic condition which affects up to 10% of the population. This high prevalence, the fact that it is usually persistent and the inherently subjective nature of the problem makes the quantitative documentation and understanding of the burden of tinnitus extremely important. The burden can be reflected by its effect on the patient's own life as well as the overall quality of family life. The aim of this study is to evaluate the effectiveness of the rehabilitation protocols used by the Nottingham Tinnitus Clinic by measuring how tinnitus affects the quality of life of the individual reporting tinnitus and the family.

Many outcome measures offer useful general health profile scales for measuring different aspects of quality of life. The SF-36 which was used in this study is one such well known index which measures health related quality of life (HRQL) in several aspects. Drummond (1997) [1] points out that the difficulty with such instruments is that they do not produce a single figure measure of quality of life. It is therefore difficult to make comparisons when

improvements are made in different dimensions of the instrument. For example it is not possible when using these scales to say that an improvement in mobility is preferable to an improvement in psychological aspects. It is also difficult to compare between different programs if a decision maker is attempting to make informed choices in order to allocate scarce funds. Furthermore the methods of scoring are not based on preferences of individuals therefore it is not possible to judge whether higher scores are associated with outcomes which are preferred by patients. In addition these types of outcome measures do not lie on a scale between 0 (dead) and 1 (healthy) so it is not possible to combine quantity of life with quality of life in the same way as the Quality Adjusted Life Year Approach (QALY).

John Brazier (1993) [2], (1998) [3] has developed a method of translating the quality of life dimensions of the SF-36 into a single figure measure of HRQL which is intended to measure the Utility of Health of the individual. The health economics concept of Utility of Health is a notion based in Economic Theory which measures the satisfaction or pleasure that an individual derives from a certain health state. The method of deriving this HRQL/ utility measure uses an algorithm which maps the SF-36 responses on to a shortened version, the SF-6D. A sample of 59 health states were valued using

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two techniques, Visual Analogue Scales (VAS) and Standard Gamble (SG). To derive VAS weights participants are requested to value each health state on a scale where 0 represents the worst health state (usually death) and 1 represents the best health state, reflecting relative values of the states according to the feelings of the participants. Standard Gamble techniques require respondents to make choices between two alternatives. The first is to live in a chronic health state for 10 years and the second is an intervention which may give full health for 10 years or fail and result in immediate death. Probabilities are assigned between the possibilities of the second choice and varied until the participants indicate the point where it is difficult to choose. The SG technique is considered by Health Economists to be a valid method of eliciting measures of HRQL/Utility because it is consistent with Von Neumann/Morgenstern utility theory (1944) [4]. Full details of the methods used are published in Brazier (1998) [3].

This study aims to test: (i) whether the effects that tinnitus has on quality of life are systematically reflected in the SF-6D by examining the differences between the general population and the tinnitus patient population; (ii) whether there is any difference between those who have been referred for a specialist tinnitus consultation and those who have had an appointment and been discharged by examining the whether the SF-6D health related quality of life and quality family life questionnaire shows any differences between the populations.

Methods

There were three populations used for this study. The first was a population sample taken from the post code address file for postal regions in Manchester and Glasgow. This initial random sample was stratified by reported hearing problem and age after a postal survey (response rate 70%, $n = 10,318$) and 1301 people were interviewed in their own homes of whom 974 fully complete the SF-36 questionnaire. The second population was all those people on the waiting list for an appointment at the Nottingham Tinnitus Clinic ($n=101$) in Autumn 1997. The third population was the set of people who had attended the Nottingham Tinnitus Clinic and who had been discharged. A sample of 1 in 4 of this population was drawn giving us 300 people. All those in the latter two populations were sent a set of questionnaires in the post as previously described (El Refaie *et al.*, 1999) [5]. These included the SF-36 questionnaire and the Quality of family life questionnaire. Analysis of the data from the SF-36 questionnaire was done using two methods, the first depending on the direct scores of the eight sub scales of the questionnaire (Ware *et al.*, 1994) [6], and the second using a preference-based single index (SF-6D, Brazier *et al.*, 1998) [3].

Only those patients who had filled in every item on the questionnaires were used in the analysis. This amounted to 974 from general population

(75%), 69 from those on the waiting list (71%) and 150 of those who were discharged (50%). There were no differences for the discharge population among those who did or did not fill in all there questionnaire in terms of age, sex or hearing thresholds. Those who did not reply were significantly more likely to have less annoying tinnitus ($\chi^2 = 32$, $df = 3$, $p < 0.001$). Those who did not reply in the other two populations were older (by about three years on average) and had slightly worse hearing (by about 5 dB HL over the 0.5, 1, 2 and 4 kHz average).

The analyses reported here were carried out using the GLIM system for model comparison, P-Stat for univariate statistics and SPSS v9.0 for Windows to conduct the factor analysis. The general population stratified random sample was weighted to the overall populations characteristics in terms in age and sex. The other two samples used a weight of one per case. Comparison between the two study groups as well as a reference group derived from the general population was performed in GLIM, with adjustment to the reported hearing disability, age, sex and tinnitus annoyance level.

Results

The single value SF-6D utility estimate for the general population was 0.908 (approximate 95% ci 0.902–0.913), for the standard gamble derived estimate (SG) and 0.677 (0.664–0.690) for the visual analogue derived estimate (VAS). This compares well with the data derived in a previous independent study [7] where the values for male and female for SG estimates were 0.933 and 0.910 compared with 0.924 (0.917–0.932) and 0.893 (0.884–0.901) in this study. The VAS estimates were 0.730 and 0.674 for male and female respectively compared with 0.714 (0.697–0.732) and 0.647 (0.629–0.665) in this study. Figure 1 shows the SF-6D SG estimates as a function of study and self-reported tinnitus annoyance. The SF-6D score decreases significantly with tinnitus severity in all three populations ($F(4,939) = 23.2$, $p < 0.001$; $F(2,66) = 3.1$, $p < 0.05$; $F(3,146) = 7.0$, $p < 0.002$, respectively).

The general population SF-6D SG estimate of 0.93 is a reasonable baseline against which to measure the effects of tinnitus and hearing problems. However, these univariate scores whilst giving a clear picture with respect to severity of tinnitus report do not necessarily give an accurate picture with respect to the comparisons between groups because of the very different proportion of people in different age groups and with different reported hearing problems in each group. It is necessary to perform a multivariate analysis to establish the difference between groups, taking into account not only the degree of tinnitus annoyance but also age, sex and hearing status.

Table 1 reports the parameters derived from such an analysis conducted in GLIM (using normal error assumptions) for the SG means estimates and VAS estimates of the SF-6D health utility index. The

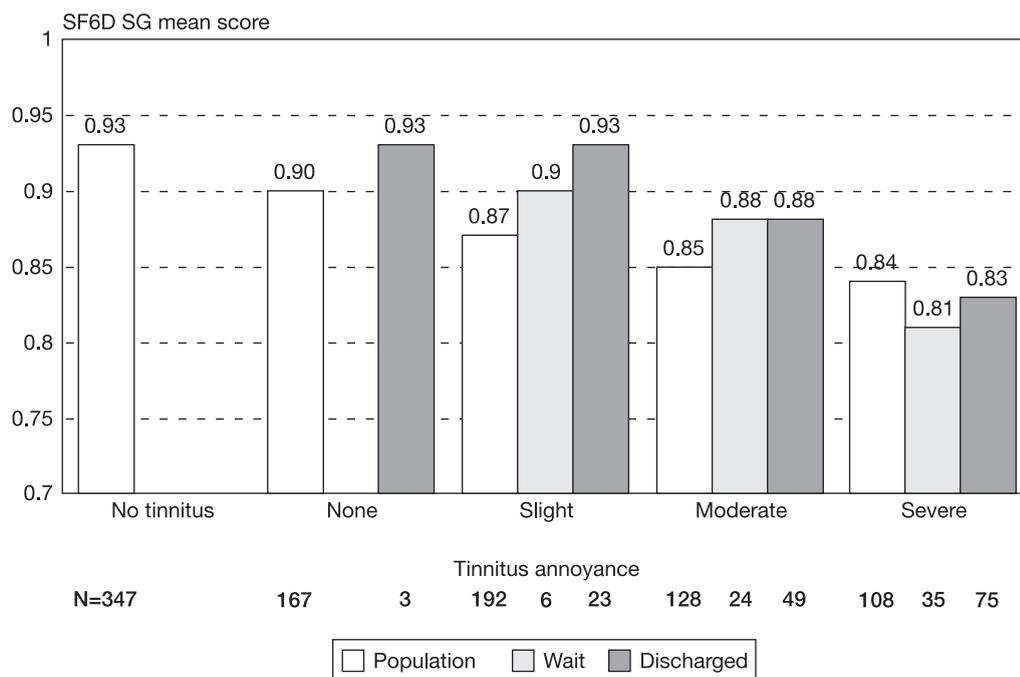


Figure 1 The SF-6D values as a function of tinnitus annoyance for a general population sample and for two clinic samples (a) on the waiting list to be seen and (b) seen and discharged. The number in each category is shown below the x-axis.

Table 1 Parameter estimates, with 95% confidence intervals and probability values, from the GLIM model of SF-6D single value health utility estimates derived from the SG and VAS methods. The Baseline estimates are explained in the text. All main effects were statistically significant ($p < 0.05$).

| Outcome variable | Parameter | Value | Low CI | Upper CI | Prob. |
|---------------------------|---------------------------|----------|--------|----------|-------|
| SG MEAN | Baseline | 96.1 | 94.8 | 97.3 | 0.000 |
| | Age 40-49 | -1.1 | -2.6 | -0.5 | 0.092 |
| | Age 50-59 | -4.9 | -6.6 | -3.2 | 0.000 |
| | Age 60-69 | -3.6 | -5.3 | -1.9 | 0.000 |
| | Age 70+ | -3.5 | -5.2 | -1.8 | 0.000 |
| | Female | -3.4 | -4.5 | -2.3 | 0.000 |
| | Hearing problem level (2) | -1.0 | -2.8 | -0.8 | 0.137 |
| | Hearing problem level (3) | -5.1 | -7.6 | -2.6 | 0.000 |
| | Hearing problem level (4) | -7.8 | -11.6 | -3.9 | 0.000 |
| | Tin annoy level (2) | -2.0 | -3.5 | -0.4 | 0.006 |
| | Tin annoy level (3) | -3.6 | -5.3 | -1.9 | 0.000 |
| | Tin annoy level (4) | -4.8 | -7.0 | -2.6 | 0.000 |
| | Tin annoy level (5) | -7.3 | -9.7 | -4.8 | 0.000 |
| | Patient on waiting list | -0.8 | -2.0 | -3.7 | 0.287 |
| | Patient discharged | -3.2 | -1.0 | -5.4 | 0.002 |
| | VAS MEAN | Baseline | 79.8 | 77.3 | 82.3 |
| Age 40-49 | | -0.6 | -2.6 | 3.8 | 0.356 |
| Age 50-59 | | -8.9 | -12.4 | -5.4 | 0.000 |
| Age 60-69 | | -9.2 | -12.7 | -5.7 | 0.000 |
| Age 70+ | | -10.5 | -14.1 | -7.0 | 0.000 |
| Female | | -7.9 | -10.2 | -5.7 | 0.000 |
| Hearing problem level (2) | | -4.6 | -8.4 | -0.9 | 0.007 |
| Hearing problem level (3) | | -12.2 | -17.3 | -7.1 | 0.000 |
| Hearing problem level (4) | | -14.3 | -22.3 | -6.3 | 0.000 |
| Tin annoy level (2) | | -4.5 | -7.7 | -1.3 | 0.003 |
| Tin annoy level (3) | | -7.1 | -10.7 | -3.6 | 0.000 |
| Tin annoy level (4) | | -10.2 | -14.7 | -5.6 | 0.000 |
| Tin annoy level (5) | | -17.5 | -22.6 | -12.5 | 0.000 |
| Patient on waiting list | | -1.5 | -4.4 | -7.3 | 0.314 |
| Patient discharged | | -6.1 | -1.5 | -10.6 | 0.005 |

parameters have been multiplied by 100 for ease of reference and are referred to as health utility percentage points. There were five design factors in the analysis, but not every level of each factor was crossed with every other factor, e.g. because it is not likely for someone on the tinnitus clinic waiting list to say that they do not have tinnitus or that it does not annoy them. The factors were age: (five levels; <40, 40–49, 50–59, 60–69, 70+); sex (two levels; male and female); reported hearing difficulty in quiet in the better hearing ear (four levels; no problem, slight, moderate, severe or total); reported tinnitus annoyance (five levels; no tinnitus, no annoyance, slight, moderate and severe annoyance); and population type (three levels; general population, patient waiting list, patient discharged). The first listed of each factor was taken as the baseline against which the parameter estimates were compared. For instance in the analysis for the SG mean a person in the age range 70+ yrs would have a SG mean health utility index that was 3.5 percentage points less than the mean for the group that was <40 yrs. Thus the mean estimate of those 70+ yrs would be 92.7. The baseline is the estimate of the group that is <40 yrs, male, no hearing or tinnitus problem from the general population. From Table 1 there is seen to be a main effect of age, sex, hearing problem, tinnitus and population status for both the SG and VAS derived health utility index. The effect of tinnitus annoyance and of hearing disability appear to be monotonic. The group who report severely annoying tinnitus have a utility that is some 7.3% less than the baseline for the SG measure and 17.5% less for the VAS derived measure. There is no difference between the general population who have a severely annoying tinnitus and the general population on either measure. However there is a significant difference between those who have been discharged and the general population of about 3.2% for the SG measure and 6.1% for the VAS measure when the other four factors were taken into account. The populations SD for the SG mean is of the order of 9% and for the VAS measure is 20%. The effect of severe tinnitus is therefore of the order of 0.8 of a standard deviation, which is a relatively big effect. A moderately annoying tinnitus gives a half standard deviation effect. Because of the relatively small numbers in the patient groups, it has not been possible to look comprehensively at whether there are substantial second and third order interactions that would help us interpret the present findings.

The impact of tinnitus on quality of family life (QOFL) was examined using our QOFL questionnaire. We examined the dimensionality of this questionnaire using factor analysis (a principal components analysis, based on the correlation matrix, was used with a final stage being varimax rotation of the resulting factor structure). Six factors were found in the questionnaire which are reported, together with the factor loadings, in Table 2. The first rotated factor accounts for 18% of the variance and has large loadings on eight questions that reflect day to day activities in which families might engage

(e.g. enjoying going out together; watching TV together etc). The second factor accounts for 15% of the variance and loads on seven questions concerning the effects of tinnitus on the patient (e.g. embarrassment or worry about the condition etc). The third factor accounts for 12% of the variance and loads on six questions and is concerned with the effects on family life (e.g. money, control and view of the future). The fourth factor accounts for ten percent of the variance with the final two factors each accounting for an additional five percent. Overall the factor model accounts for about 66% of the variance, which is reasonably good. Each of the QOFL factor scores was analysed separately in GLIM taking into account age, sex and reported hearing impairment.

Table 3 shows that there were main effects of severity of tinnitus, after these demographic and hearing influences had been modelled for factors four and six. These were the items that were concerned with coping with day to day activities and also restricted activities. There was a significantly better QOFL score for the discharged patients for two factors: (i) effect of tinnitus on the patient; (ii) understanding of tinnitus, but there was one factor (factor 1) that had a decrement which was the day to day activity with the patient.

Discussion

The overall population score on SF-6D in this study is very similar to that obtained in a benchmark study (Brazier *et al.*, 1998) [3]. The patients on the Nottingham Tinnitus clinic waiting list had SF-6D SG scores of about 0.84, some 0.09 less than the no tinnitus general population (about 1 SD less), and a VAS score of 0.50 which was 0.18 less than the baseline. In the benchmark study osteo-arthritis of the knee was also studied and the SG estimate was about 0.75 and the VAS estimate was about 0.31 [7]. Whilst these data have not been adjusted for age, sex and social factors, it suggests that the effect of tinnitus on this measure of health utility is half that of osteo-arthritis of the knee. Nevertheless it is a large effect that is greater than that due to age, and in line with that due to hearing disability. Table 1 shows that for a female aged 65 with a severely annoying tinnitus, and a severe hearing problem in quiet on the better ear there is an expected SG utility of about 0.74. This severity profile accounts for about one in six of those who are on the waiting list which is a reasonably high proportion and therefore the burden of this group can be seen to be similar to that of the osteo-arthritis of the knee group.

The major finding with respect to the SF-6D data was that there was a significant effect of population whether the SG or VAS estimates were used. This effect took the form that those who had been discharged seemed to have a significantly greater health utility, as a group, than those who were in the general population. This effect is about 0.03 (one third of an SD). However, whilst there appears to be a difference between the two patient groups, that

Table 2 The six factors extracted from the MRC IHR quality of family life questionnaire with their loadings on individual questions.

| Factor interpretation | Questionnaire items | Factor loadings for the six factors | | | | | |
|----------------------------------|----------------------------------|-------------------------------------|-------|-------|-------|-------|-------|
| | | 1 | 2 | 3 | 4 | 5 | 6 |
| Day to day activity with patient | Enjoy meals together | 0.817 | | | | | |
| | Enjoy going out together | 0.769 | | | | | |
| | Enjoy spending time together | 0.747 | | | | | |
| | Enjoy holidays together | 0.743 | | | | | |
| | Family happiness | 0.703 | | | | | |
| | Enjoy TV together | 0.655 | | | | | |
| | Coming to agreement | 0.568 | | | | | |
| | Support from people | 0.434 | | | | | |
| Effect of tinnitus on patient | Worried about communication | | 0.870 | | | | |
| | Help to communicate | | 0.786 | | | | |
| | Danger because of tinnitus | | 0.727 | | | | |
| | Difficulty enjoying TV | | 0.593 | | | | |
| | Worried about well-being | | 0.580 | | | | 0.414 |
| | Embarrassed during activities | | 0.573 | | | | |
| | Stress during activities | | 0.567 | | | | |
| Effect of tinnitus on patient | Money to keep standard | | | 0.742 | | | |
| | Needs being met | | | 0.697 | | | |
| | Control over life | | | 0.574 | | | |
| | Satisfied with achievements | | | 0.551 | | | |
| | View of future | | | 0.524 | 0.434 | | |
| | Under pressure | | | 0.462 | | 0.401 | |
| Coping with day to day life | Household activities | | | | 0.732 | | |
| | Coping in general | | | | 0.679 | | |
| | Coping in future | | | | 0.664 | | |
| | Time for social activities | | | | 0.578 | | |
| | Time to get ready in the morning | | | | 0.438 | | |
| | | | | | | | |
| Understand of tinnitus | Understand about tinnitus | | | | | 0.706 | |
| | Interfere in your life | | | | | 0.648 | |
| Restrictions on activity | Restricted in choice of holiday | | | 0.478 | | | 0.580 |
| | Restricted in going out | | | | | | 0.532 |

Notes: Extraction Method: Principal Component Analysis. Rotation Method: Varimax with Kaiser Normalization. Rotation converged in 8 iterations.

Table 3 Parameter estimates, with standard errors, for effects of tinnitus severity and of population on the six factors extracted from the MRC IHR quality of family life questionnaire.

| Quality of Family Life Factor | Moderate annoying tinnitus | | Severely annoying tinnitus | | Discharged vs Waiting list patients | |
|----------------------------------|----------------------------|-------|----------------------------|-------|-------------------------------------|-------|
| | Estimate | s.e | Estimate | s.e. | Estimate | s.e. |
| Day to day activity with patient | 0.25 | 0.22 | -0.17 | 0.22 | -0.31 | 0.16* |
| Effect of tinnitus on patient | 0.10 | 0.19 | -0.20 | 0.19 | 0.38 | 0.14* |
| Effect of tinnitus on family | 0.03 | 0.23 | -0.12 | 0.23 | 0.16 | 0.17 |
| Coping with day to day life | -0.58 | 0.22* | -0.69 | 0.22* | -0.14 | 0.16 |
| Understanding of tinnitus | -0.16 | 0.22 | -0.35 | 0.22 | 0.39 | 0.16* |
| Restriction on activities | 0.08 | 0.22 | -0.46 | 0.22* | 0.03 | 0.16 |
| Overall score | -0.05 | 0.12 | -0.46 | 0.13* | 0.09 | 0.09 |

Notes: The effects of age, sex and hearing status have been controlled in this analysis. *indicates that a parameter is statistically significant at the $p < 0.05$ level.

contrast was not significant, as the effect is too small to detect with the numbers used here. The conclusions we can draw would be stronger if the two patient groups were significantly different. However, we can interpret these findings as reasonably good cross sectional and retrospective evidence that

there is overall positive utility in the tinnitus consultation that is measurable by the SF-6D. This suggests that the SF-6D could be part of a cost-effectiveness appraisal of interventions for tinnitus. A longitudinal study, which we are currently conducting with those on the waiting list, should enable

a better interpretation of these data and a possible insight into the importance of different aspects of the consultation.

The quality of family life results show that there is indeed structure to the impact of tinnitus on the family. The six factors that were found in terms of the 'state' of family life when the questionnaire was filled in seem to carry some face validity. Two of the factors vary with severity of the tinnitus, after demographic and hearing status were controlled. These two factors reflect the coping strategies of the family and the extent to which they feel restricted in their choices when for instance getting up in the morning or going out. However, the other four factors do not show a severity gradient with tinnitus annoyance (other markers of tinnitus severity from our questionnaire correlate with factors 2 to 6, however as present there does not seem to be any marker of tinnitus severity that correlates directly with factor 1 – day to day activity of the patient).

The population who have had their session(s) at the Nottingham tinnitus clinic are significantly different on three of the factors. It is interesting that whereas those with severe annoyance do have a significantly worse overall score in terms of quality of family life (a simple percentage of the score obtained out the total possible on the questionnaire) there was no effect of population on the overall score. That is in part due to the fact that two of the significant effects found here seem to increase quality of family life there is one factor where the effect is in the other direction. So whereas the impact of the tinnitus on the patient (factor 2) is reduced, e.g. in terms of worry and the understanding of tinnitus (factor 5) is greatly increased (as one might hope) there is a negative effect on the day to day activity of the patient, e.g. family agreement, enjoyment of a number of activities. This is an interesting finding which may suggest that whilst worry in general is decreased and doubt about the cause of the tinnitus and its origin may be put to rest the impact on core activity is not always in the direction that might be expected. The overall estimate of quality of family life was also estimated using a Euroquol thermometer where the state of quality of family life was represented as being 100 if it was the best imaginable and 0 if it was the worst imaginable. There was a significant difference ($t = 2.05$, $df = 193$, $p = 0.042$) between the two populations such that those on the waiting list had an estimate of 65.1% (SD 21%) and those who were discharged had an estimate of 71.3% (SD 19%). This suggests that overall we can conclude that there is a significant effect of intervention on family quality of life that may derive from the knowledge that is imparted at the clinic which dissipates worry and concern about the tinnitus.

In summary, we have found that the SF-6D is a robust tool, albeit with a limited sensitivity to some of the aspects that are of interest, that could be used in the assessment of the impact of tinnitus and interventions for tinnitus. The conversion of the

SF-36 to a single value index the SF-6D is still a controversial issue. It is still in development. However the extent to which we have found agreement with previous work and the extent to which it appears to be sensitive to intervention suggests that it is an avenue that should be explored further in terms of assessing the impact of tinnitus on groups of individuals and interventions to improve their health related quality of life. In terms of impact on patients the extreme 10–20% of tinnitus patients in Nottingham were shown to have an effect on the SF-6D equivalent to that reported for osteoarthritis of the knee. The MRC IHR quality of family life questionnaire seems to be a valid instrument with which to assess the impact of tinnitus on the patient's wider social context and appears to be differentially sensitive to severity of tinnitus complaint as well as showing some effects of the appointments at the Nottingham tinnitus clinic. The results with respect to the availability of information that dispels worry and doubt in those that have been discharged are interesting. However it is difficult to interpret the apparent decrement in enjoyment the family reports in the discharge group. This warrants a more detailed analysis of the present data and will be a focus of interest in the follow up of those in the waiting list group.

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Audiometric correlates of tinnitus pitch: Insights from the Tinnitus Data Registry

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Knowledge concerning the pitch of tinnitus is important for improving our understanding of possible neural mechanisms, for evaluating treatment effects, and for ensuring the maximal effectiveness of treatment techniques. The audiological literature contains many references to the relation between hearing loss and the pitch of tinnitus; however, most investigators have relied on data from relatively small numbers of subjects for evaluating such relationships. We present data from several large patient samples to illustrate the nature and extent of the relationships between the pitch of tinnitus and the audiogram. In general the pitch of tinnitus is inversely related to the overall extent of hearing loss—normally-hearing patients tend to have the highest-pitched tinnitus while those with severe hearing impairment tend to have the lowest pitches. In previous work we have described the orderly relationship between tinnitus pitch and the audiometric configuration, which is highly significant ($p < 0.0001$). We now examine that relationship in greater detail, with added attention to sources of variability in matching the pitch of tinnitus. Variability of pitch matches within and between subjects can result from the nature of the tinnitus perception themselves, as well as from variability in the loudness of tinnitus, its vulnerability to masking from sounds encountered during the testing procedure, and other influences. In addition, the psychometric techniques for matching the pitch of tinnitus may be vulnerable to certain types of measurement bias. We will summarize relevant observations in the hope that such information will offer investigators useful insights for further basic and applied research. With the continuing improvement in neurological techniques (such as functional brain imaging) that offer an analytical approach to understanding brain mechanisms for tinnitus, it is important for knowledge about the pitch of tinnitus to be as accurate and reliable as possible.

Introduction

Knowledge concerning the pitch of tinnitus in individual tinnitus patients is important for a number of reasons. Clinical needs for pitch information include: (1) documenting a patient's presenting symptoms as part of a systematic approach to planning and managing therapy; (2) obtaining quantitative baseline assessments whenever the effects of treatments are to be monitored; and (3) planning or modifying treatment techniques involving acoustical stimulation (such as tinnitus masking) that may depend on a specific frequency relationship to the patient's tinnitus.

Basic researchers also require better information about the range and distribution of tinnitus pitch in affected populations. Such data are helpful, for

example, to investigators who study the underlying mechanisms for tinnitus. Researchers who attempt to develop animal models for tinnitus also need such information, in order to recreate the salient features of tinnitus in humans. A similar requirement applies to the effort to develop objective measures or diagnostic tests capable of confirming or denying the presence of tinnitus for litigation or compensation purposes.

In addition, there are epidemiological needs for pitch information about tinnitus—studies of issues such as the relationship between tinnitus characteristics and their negative influences on patients' health and psychiatric status. Epidemiological research to characterize tinnitus in relation to important etiological agents such as damaging noise exposure or head injury is clearly an important need. Also needed are large-scale longitudinal studies of alterations in tinnitus over time (its "natural history") as well as alterations associated with aging or with progressions in disease state (e.g. in Meniere's disease or acoustic neuroma). Although

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the pitch of tinnitus seems to be a relatively straight-forward concept, in fact measuring the pitch of tinnitus entails a number of complications, many of which result from the fact that tinnitus patients tend to have impaired hearing. Our present purpose is therefore to review the relationship between patients' tinnitus and their hearing capabilities, after which we will discuss some of the measurement difficulties that have been encountered to date. We will close by presenting a very brief glimpse of current work to develop computer-automated techniques for matching the pitch of tinnitus. We do so in the hope that general use of computer automation might stimulate more widespread standardization of tinnitus measurement methods, and in the process might also provide improvement in the reliability of tinnitus measurements.

Tinnitus pitch and the audiogram

It has been known for many years that tinnitus often accompanies hearing loss [1,2,3,4]. These reports were the first to point out that the pitch of tinnitus usually corresponds to a frequency region in which the individual's hearing is abnormal. Despite that trend, it is known that individual cases can show substantial variability in regard to the precise location of the tinnitus pitch within the frequency range of impaired hearing [5]. In view of the tendency for adventitious hearing loss to effect the high frequencies first, it is perhaps not surprising that tinnitus is often perceived as a relatively high-frequency sound. Available data from several large patient samples have confirmed that the majority of tinnitus pitch matches are above 3 kHz [6,7,8].

The quantitative data to be presented here were obtained from a large population of tinnitus patients attending the Tinnitus Clinic of the Department of Otolaryngology, Oregon Health Sciences University, during the period 1982–1991. These observations have provided more detailed knowledge concerning the relation between tinnitus and hearing loss [9]. The data were obtained from patient questionnaires, interviews and audiologic evaluations, and were submitted to a number of quality-control checks [8]. After being reviewed for completeness and consistency, the data were coded and entered into the Tinnitus Data Registry, a large research data base designed for epidemiological and other types of investigations. No data were entered into the Registry unless informed consent was obtained.

Detailed analysis of the audiometric data in the Registry has revealed a strong association between the pitch of tinnitus and the extent and range of hearing loss: Data from 1033 patients were evaluated using Principle Components Analysis, yielding three major factors that together accounted for 85% of the variance in hearing levels (HLs) for the group. Individual Factor 1 and Factor 2 scores were calculated for each patient, revealing that Factor 1 corresponded to the overall amount of hearing loss and Factor 2 represented the slopes of the audiograms

(Factor 3 indicated the extent of binaural asymmetry and will not concern us here).

The individual Factor 1 and Factor 2 scores were then compared to the patients' pitch matches. For that purpose, patients were assigned to one of 5 different pitch groups based on the frequencies they had selected as matching the pitch of their tinnitus. One-way Analysis of Variance revealed a significant inverse association between patients' Factor 1 scores and the pitch of their tinnitus ($p < 0.0001$). Factor 1 reached its highest positive values (corresponding to greatest amount of hearing loss) in patients with the lowest pitch matches (<1500 Hz) and reached its lowest negative values (corresponding to least amount of hearing loss) in those with the highest-pitched tinnitus (8500 Hz).

Figure 1 is a graphic representation of the relationship of tinnitus pitch matches to the mean audiograms of the five different pitch groupings [5]. This figure highlights the orderly relation between the pitch of tinnitus and the extent of hearing loss. The inverse relationship between pitch and hearing loss is striking, with patients having successively higher-pitched tinnitus tending to show successively better hearing. These data were interpreted as strong evidence that peripheral hearing loss exerts a significant influence on the perceived pitch of tinnitus [5].

Factor 2 (the slope factor referred to above) exhibited a more complex relationship to the pitch data, as described earlier [9]. Nevertheless it too revealed a highly significant relationship between the audiometric data and the pitch of tinnitus ($p < 0.0001$).

Further support for the concept that peripheral hearing loss is an important determinant of the pitch of tinnitus comes from an analysis of gender-based differences in tinnitus [10]. In that work, tinnitus pitch matches and audiograms were evaluated separately for male vs. female tinnitus patients. Figure 2 shows the mean hearing thresholds for the two groups and illustrates the commonly-observed trend for men to show greater hearing loss in the high frequencies (3–8 kHz) and women to show greater hearing loss in the lower frequencies (0.250–1 kHz). The pitch matches obtained for the two groups are shown in Table 1. There were proportionately more women with tinnitus pitch below 2500 Hz, and proportionately more men with tinnitus pitch at or above 8500 Hz. Statistical evaluation showed these differences to be significant ($p = 0.001$).

Although the various sets of data cited above indicate robust relationships between the pitch of tinnitus and the audiogram when measured in large groups of patients, it is also well known that within-subject variability of tinnitus pitch measurements constitutes a troubling issue. Several laboratories have therefore undertaken efforts to improve the reliability with which tinnitus pitch matches can be obtained in individual patients [11,12,13]. While large-sample techniques are capable of generating meaningful generalizations about groups of

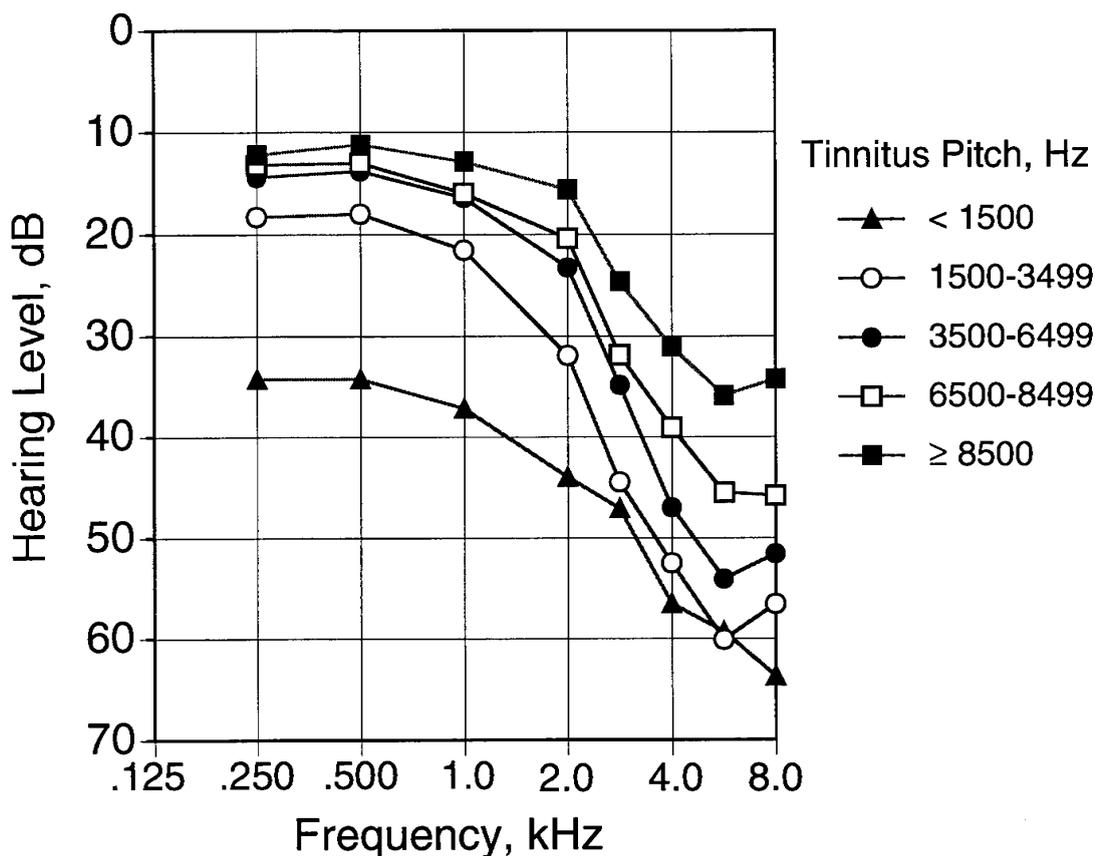


Figure 1 Relation between tinnitus pitch and the audiogram in Tinnitus Clinic patients. Mean thresholds are shown for the right ears; (because of the complexity of the graph, error bars were omitted).

Table 1 Tinnitus pitch matches in tinnitus clinic patients: males vs. females

| Pitch Match (HZ) | Males (%) | Females (%) |
|------------------|-----------|-------------|
| 100 – 1499 | 6.0 | 15.2 |
| 1500 – 2499 | 6.2 | 8.7 |
| 2500 – 3499 | 11.2 | 11.5 |
| 3500 – 4499 | 14.2 | 9.5 |
| 4500 – 5499 | 6.1 | 6.1 |
| 5500 – 6499 | 11.8 | 12.2 |
| 6500 – 7499 | 5.5 | 5.2 |
| 7500 – 8499 | 18.0 | 18.9 |
| ≥8500 | 21.0 | 12.7 |
| | 100.0 | 100.0 |

Information on the pitch of the predominant tinnitus was obtained from 803 patients (583 men, 220 women). The distributions of pitch matches differ significantly between the two groups ($p = 0.001$)

patients, at the individual level there are a number of technical issues that require attention.

Technical limitations in evaluating tinnitus pitch

It has been known for a long time that individuals' efforts to match the pitch of their tinnitus may exhibit considerable within-subject variability [14]. Although a small number of individuals can be

found who are capable of matching their tinnitus with precision and reliability, usually such individuals are musically or acoustically trained and their responses are not representative of the large majority of tinnitus patients [15].

Problems in obtaining reliable pitch matches for tinnitus can be summarized under several headings:

- (1) In many cases, pitch-matching techniques involve testing procedures that are chosen because they are expedient – that is, chosen for their simplicity and brevity – rather than for their psychoacoustic sophistication.
- (2) The subjects are often naive and have little knowledge or vocabulary concerning the dimensions of pitch, loudness, and timbre.
- (3) A large majority of tinnitus patients have substantial hearing loss that may interfere with their perception of external comparison tones, particularly tones in the higher frequencies.
- (4) A large majority of tinnitus patients have high-pitched tinnitus, requiring the use of high-pitched test tones to identify an appropriate matching stimulus. Such tones are relatively lacking in tonality, thus making it more difficult for the subject to determine when a good match to the tinnitus has been obtained.
- (5) As a consequence of items (3) and (4) above,

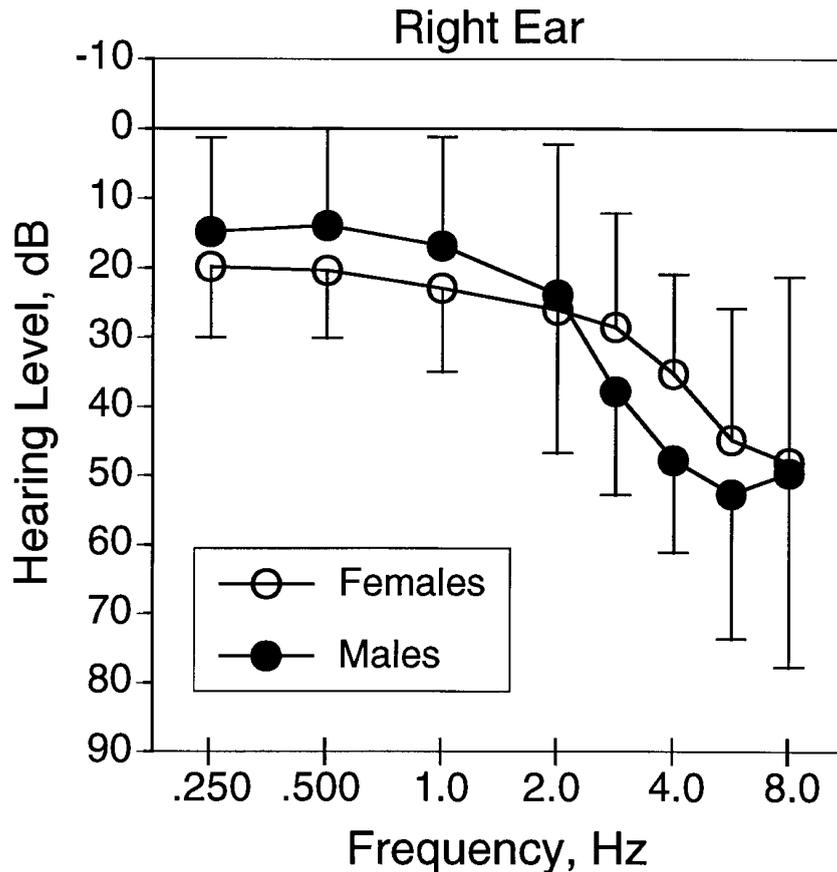


Figure 2 Mean hearing thresholds for male and female tinnitus clinic patients

Note: Thresholds for the right ears are shown. The statistical interaction between gender and stimulus frequency (men's hearing better below 2 kHz, women's hearing better above 2 kHz) was statistically significant ($p < 0.0001$).

the test equipment may prove to lack adequate frequency range and/or sufficient sound output to generate stimuli that are comparable to the patient's tinnitus.

Added to the problems described above is the inherent complexity and/or variability that characterizes tinnitus itself. Detailed data have been reported concerning the spectral composition of tinnitus perceptions in a large group of tinnitus clinic patients, showing that approximately 40% of tinnitus patients hear two or more tinnitus sounds [16]. Even among those who reported only one tinnitus sound, a substantial percentage reported that their tinnitus resembled spectrally-complex sounds such as "crickets", "hissing", "ocean roar", and other sounds heard in nature. The task of identifying an external tone that appears equivalent in pitch to the subject's internally-perceived tinnitus sound(s) is likely to be more difficult if the subject's tinnitus is spectrally complex. Although it is usual for examiners to ask patients with multiple tinnitus sounds to match only their "predominant" tinnitus sound, it is probable that the task of identifying an external matching tone is made more difficult by the presence of several different internal sounds.

Another problem is caused by actual variations in the loudness and tonal quality of an individual's

tinnitus. Data on the prevalence of such variations in a large sample of tinnitus clinic patients indicated that approximately 3/4 of tinnitus patients notice loudness fluctuations, usually occurring spontaneously, and approximately one-third notice variations in the sound quality of their tinnitus [17]. In such cases, the task of identifying an external tone that matches the tinnitus is in effect an attempt to hit a moving target.

The variability of tinnitus pitch matches is certainly influenced by the choice of test procedure. Considerable effort has been devoted to exploring variations in testing techniques, in the effort to develop methods that would maximize the precision and reliability of individual patients' pitch matches [11,12,13]. For example lower variability was observed for tinnitus pitch matches when the pitch-matching procedure involved a forced-choice "double-staircase" method than when it involved the Method of Adjustment [11]. One problem with applying such methods with tinnitus clinic patients, however, is that much of the research has involved laborious psychoacoustic protocols requiring a number of hours or even multiple test sessions in order to allow the subjects to become familiar with the testing task. Such lengthy and elaborate testing routines are not feasible for use in tinnitus clinics where patients do not readily submit to extended

psychoacoustic tests, nor do the clinics have adequate resources to support such testing. It should be acknowledged, however, that these lengthier psychoacoustic protocols, while not adapted for use in epidemiologic work or in clinical practice, might be of definite value for very precise definition of tinnitus characteristics in certain types of research—such studies as high-resolution brain imaging in tinnitus patients, or other detailed tests where only a few subjects are to be studied.

Many investigators have commented on the need for careful adjustment of external comparison tones to match the loudness of the patient's tinnitus, so that the pitch-matching task involves only pitch differences and is not confounded by loudness differences between the tinnitus and the external tones [18,19]. To facilitate equal-loudness comparisons during pitch-matching, Vernon has developed a two-alternative forced-choice method in which successive pairs of tones, each of which is first adjusted to be equal in loudness to the tinnitus, are presented and the patient is asked to choose which one of the pair sounds more like the tinnitus [20]. Mindful of the well-known observation that tinnitus is customarily perceived at low sensation levels, he has also commented on the fact that frequency discriminations at such low levels are difficult even for normal subjects. It is significant that the available data on frequency difference limens for external tones, obtained in hearing-impaired subjects, are typically measured at considerably higher sensation levels [21,22]. When normally-hearing subjects without tinnitus were required to match the pitch of external tones presented at only 5 dB SL, they were found to have great difficulty in obtaining reliable pitch matches [14]. His conclusion was that the ability of tinnitus patients to achieve reliable pitch matches for their tinnitus is necessarily compromised by the low sensation levels at which the pitch-matching must be done.

"Octave confusion" is another possible source of unreliability in pitch matching for tinnitus [23,24]. It is well known that octave errors are a common form of pitch confusion observed in normally-hearing subjects, even those who are musically trained and possessed of excellent pitch discrimination ability. To prevent octave confusions in matching the pitch of tinnitus, the two-alternative forced-choice procedure described above provides an effective method for presenting comparison tones spaced an octave apart to allow the subject to choose which one best matches the tinnitus [20]. One caveat, however, is that in some cases the patient's tinnitus may actually consist of two or more tones separated by octave intervals. That possibility is consistent with the observations cited above that many patients report tinnitus that sounds spectrally complex.

Among the many other factors that could contribute to test-retest variability of tinnitus pitch matches, impaired frequency discrimination ability and binaural diplacusis are both likely contributors to the measurement variability in tinnitus patients who are hearing-impaired. Although these condi-

tions would certainly be expected to reduce individuals' accuracy in identifying frequencies that match the pitch of their tinnitus, confirmation through direct measurement in tinnitus patients is lacking and thus these suggestions remain conjectural at present. Clearly, research to explore these possibilities would be of value.

Finally, the presentation of external comparison tones can by itself cause changes in tinnitus and thus lead to increased measurement variability of tinnitus pitch matches. The phenomenon of residual inhibition (temporary reduction or suppression of tinnitus by external sounds) has been found to occur in close to 90% of all tinnitus patients [25]. Given appropriate stimulation by external tone(s), it seems quite likely that residual inhibition frequently causes significant interference with attempts to obtain reliable pitch measurements.

An interesting example of interference by residual inhibition was reported in work with arthritis patients whose tinnitus resulted from use of non-steroidal anti-inflammatory drugs (R. Brummett, personal communication). Many of these patients had mild or "borderline" tinnitus that proved to be so easily suppressed by weak ambient sounds in the testing environment that pitch-matching could not be done. It is important for examiners and patients alike to be aware that subtle influences such as these can interfere with their ability to obtain reliable pitch matches.

The occurrence of residual inhibition in the tinnitus-testing situation is not limited to cases of mild tinnitus. Some patients with "loud" tinnitus experience residual inhibition very easily, a fact which can be used to great therapeutic advantage [19]. Because residual inhibition is not usually produced by contralateral stimulation, it is evident that unintended residual inhibition can be avoided if the comparison tones during pitch-matching are presented to the contralateral ear whenever possible [23,26]. Another important testing detail to minimize residual inhibition is to present the external comparison tones in *ascending* intensities, using small steps (1–2 dB) [14]. However, residual inhibition may be difficult to avoid in patients who have bilateral tinnitus, hence a possibility that remains to be investigated is whether residual inhibition in fact constitutes a significant source of unreliability in tinnitus pitch-matching.

Computer-automated techniques for matching the pitch of tinnitus

Several clinics have recently initiated efforts to develop computer-assisted techniques for measuring the pitch of tinnitus [26,27]. These techniques are particularly valuable because they make it possible to standardize the testing techniques across different test environments, and also relieve the examining staff from some of the time demands and repetitive burden of personally conducting the individualized tinnitus tests. Because of the greater ease with which large numbers of patients may be tested,

automated techniques also facilitate presentation of a number of identical repetitions of the same test to each of the patients, thus permitting study of test-retest reliability.

In one recent example of computer-assisted techniques [26], testing sessions lasted from 45 to 70 minutes and included automated measurement of thresholds and tinnitus loudness matches at 12 frequencies separated by 1/3 octave intervals. In addition, minimum masking levels were measured at each frequency and the pitch of tinnitus was matched using a two-alternative forced-choice procedure. The patients were required to move a spring-loaded lever to indicate their responses to the test stimuli. The protocol included warm-up and practice time to reduce response variability. Analysis of the test-retest reliability was conducted for a group of 25 tinnitus patients, indicating good reproducibility of the pitch matches using this computer-automated method. A different approach to computer-assisted testing techniques has recently been developed at the Veterans Affairs National Center for Rehabilitative Auditory Research [27]. Three different testing protocols were evaluated in 42 individuals with tinnitus, including measures of thresholds, tinnitus loudness matches at frequencies from 1–16 kHz, and tinnitus pitch matches. The computer setup involved a custom-designed graphical user interface with a touch-sensitive monitor for patients to use in registering their responses to the test stimuli. The aim was to determine whether there were significant differences between the three different test protocols in regard to test-retest reliability or the amount of testing time required. The work provided an efficient comparison of the three testing methods and also generated useful information about individual response variability. Thus, in addition to its use in developing standardized test protocols that can be implemented widely for use in a variety of tinnitus clinics, the computer techniques provided insights into individual patients' response patterns and thus may prove useful for determining the validity of claims for compensation. The subjects in these experiments ranged from 39 to 83 years of age, thus indicating that use of the automated technique is practicable for a wide range of subjects.

Summary

It is clear from the foregoing discussion that a great deal of thought and considerable ingenuity have been applied to development of pitch-matching methods for tinnitus. The current interest in computer-assisted measurement techniques is a hopeful sign that such innovation will be maintained and thus provide even more refined techniques than those that have emerged over the past two decades of tinnitus testing. Computer-automated methods could offer greater objectivity in presenting test stimuli and recording the resulting responses, as well as facilitating the

standardization of testing techniques for better comparison between data obtained in different clinics. With the continuing improvements in neurological techniques (such as functional brain imaging) that offer an analytical approach to understanding brain mechanisms for tinnitus, it is incumbent on tinnitus researchers to provide knowledge about the pitch of tinnitus, and its relation to the individual's hearing status, that is as accurate, detailed, and reliable as possible.

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Prevalence and problems of tinnitus in the elderly

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The Australian Longitudinal Study of Ageing (ALSA) provides self report and performance based measures of sensory function and selected socio-demographic, physical, cognitive and psychosocial information in a large sample of elderly urban Australians (N = 2087), aged 70–103 years. This study examines tinnitus in 1453 ALSA respondents, who provided data about tinnitus at baseline and at follow-up 2 years later.

Two hundred and fifty eight respondents (17.6%) reported tinnitus on both occasions; 64.8% reported no tinnitus on either occasion and the remainder reported tinnitus only at baseline (10.6%) or only at follow-up (7.0%). Overall, respondents with tinnitus performed more poorly on tests of measured hearing, and appear to experience a lower quality of life in several domains than respondents who do not report tinnitus.

Introduction

A need for greater awareness of tinnitus among health professionals and improved expertise in its management will increase as the number of people with tinnitus grows. The well established association between the perception of tinnitus and the degree of hearing impairment [1,2] means that tinnitus is more likely to become apparent to older people. With a significantly increasing proportion of older people in the population in developed nations, further consideration of tinnitus in relation to old age is timely. Keys to potential effectiveness in the areas of health services planning and the delivery of clinical services to older individuals with tinnitus are: (1) better prevalence data in the specific population of old and very old people, (2) greater understanding of the natural history of tinnitus, and how old age may modify it, and (3) more knowledge about the effects of tinnitus in old age.

The National Study of Hearing in Britain [3] reported prevalence rates for Prolonged Spontaneous Tinnitus (PST) of 13.3% for men and 13.1% for women. The prevalence of PST peaked at 19.0% for those in age group 61–70 years but barely dropped in the two successive age groups, 71–80 and 81–99 years.

Clinical data about first presentation at specialist

tinnitus clinics consistently show the majority of patients are 50–70 years of age. This age range represented 51% of the patients at a large tinnitus clinic in the United States [4] and 59% of the patients attending a comparable clinic in Wales [5]. Those over 70 years comprised 10% of the American patients and 17% of the Welsh patients.

Rosenthal and Karlsson [6] found the overall percentage of tinnitus of any type was 27%–34% at age 70 years. This increased to 52% of men and 36% of women at age 79 years. Both men and women who experienced tinnitus had poorer hearing, their median audiometric thresholds at all test frequencies being higher (that is, poorer) than those with no tinnitus or those with occasional tinnitus. This effect was greater for men than for women.

Rubinstein, Osterberg and Rosenthal [7] tracked individuals reporting tinnitus from 70 years of age and found substantial longitudinal fluctuations in tinnitus at ages 75 and 79, with some spontaneous remission. The proportion at each investigation time reporting continuous tinnitus appeared to be more stable (7.7%, 11.5% and 11.2% at ages 70, 75 and 79 years) with greater variability in the proportions reporting occasional tinnitus (19.9%, 16.7% and 31.1% respectively). Occasional tinnitus showed an increase with age but continuous tinnitus did not despite the expected increase in age related hearing loss. The authors emphasised the importance of these preliminary data to the generally accepted view of tinnitus as a “rather stable condition with uncommon spontaneous remission” (p.154).

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Vernon and Press [8] found that the proportion of older people, those over 65 years on a tinnitus data registry, who reported having tinnitus for less than one year (around 20%) was only slightly less than the proportion of younger people, those under 50 years, who reported tinnitus of this duration.

Sanchez and Stephens [5] investigated self-reported difficulties associated with tinnitus in a large sample of patients. They found no diminution in the average number of complaints volunteered with advancing age, nor were there differences between the auditory and non-auditory tinnitus related complaints of patients in the oldest age group, 70 years and older ($N = 76$) and those in three younger age groups. However, Scott *et al.* [9] found that with increasing age and increased duration of tinnitus, the number of subjects who regarded tinnitus as their main problem decreased. Accordingly, Swedish subjects, 66 years and older who had tinnitus, were less interested in undergoing treatment than subjects in two younger age groups. Depression and insomnia were the psychosomatic factors which most strongly predicted increased discomfort from tinnitus and decreased tolerance.

The studies reviewed suggest greater variability in the way individuals experience tinnitus in old age than has been assumed and the broad dimensions of tinnitus related complaint and adaptation in old age are possibly even more complex than in younger people.

Methods

Participants

Participants were 1453 community-dwelling older adults who took part in Wave 1 of the Australian Longitudinal Study of Ageing (ALSA; Centre for Ageing Studies, 1992) [10] and in Wave 3 two years later. Of these 758 were male and the mean age was 78.1 years ($SD = 5.9$, range 70 to 103). Subject selection was from a randomised stratified sample of older adults living in the metropolitan area of Adelaide, South Australia. The present sample of 1453 represents around 70% of the original pool of 2087 participants.

Measures

Auditory characteristics

Tinnitus. At each wave respondents were asked questions about tinnitus to establish its presence or absence and, if present, its frequency. In Wave 1 these were: "Do you have ringing or other noises in your ears and head?" (Possible responses: Yes or No) and "How often do you hear ringing or other noises?" (Possible responses: Occasionally – less than once per week; Frequently – more than one per week; Constantly). In Wave 3, the two questions were collapsed together into: "Do you ever get noises in your head or ears which usually last longer than 5 minutes?" (Possible responses: No, never; Some of the time; Most or all of the time).

Measured hearing. Pure tone audiometry averages (PTA) for the better (BEPTA) and worse (WEPTA) ear were calculated at each wave across 0.5, 1, 2 and 4 kHz. This yielded four indices of measured hearing, Wave 1 BEPTA, Wave 3 BEPTA, Wave 1 WEPTA and Wave 3 WEPTA. Where respondents had only one functioning ear, this was taken as the better ear. Thus BEPTA data were available for 846 participants, and WEPTA data for 805 participants.

Self-reported hearing difficulties. At Wave 1 respondents were asked to indicate the extent to which they experienced auditory difficulties or had accessed health services in relation to these difficulties. These are displayed in Table 4. For the purposes of the present study most self-reported hearing variables were converted to categorical variables with two levels (1 = Yes, complaint is present, 2 = No, complaint is absent). In many instances self-reported hearing variables were not comparable between Waves 1 and 3. Consequently, only the results for Wave 1 are reported here.

Non-auditory characteristics

Sleeping difficulties. Respondents were asked the extent to which they experienced difficulty falling asleep, difficulty with early morning wakening and trouble with waking at night (for all variables 1 = never, 5 = always).

Self-rated health. Respondents rated their overall health on a 5-point scale (1 = excellent, 5 = poor).

Depression. Depressive symptomatology was measured using the Center for Epidemiology Depression Scale (CESD; Radloff, 1977) [11]. The CESD is a 20-item inventory in which respondents are asked to rate how often during the previous week (0 = never, 3 = almost always) they have experienced particular states associated with depression. A score of 16 or above indicates the possible presence of clinical depression.

Procedure

The question domains described above were part of an extensive face to face interview carried out on each occasion in the respondent's home. Those who agreed to participate in the clinical data collection carried out home based audiometric testing on a separate occasion within a few weeks of the interview. Air conduction thresholds were determined under earphones for octave frequencies from 0.5 to 8 kHz, and half octave frequencies 3 and 6 kHz in each ear.

Results

Analytic strategy

For most analyses, participants were classified into one of four age groups on the basis of their age at Wave 1, 70 to 74 years, 75 to 79 years, 80 to 84 years and 85 or more years (mean age = 77.9). For

Table 1 Presence or absence of tinnitus by sex and age group

| Tinnitus Status | Age Category | Sex | | Total | % Age Group |
|--------------------|--------------|------|--------|-------|-------------|
| | | Male | Female | | |
| 1. Absent W1, W3 | 70-74 | 141 | 169 | 310 | 64.9 |
| | 75-79 | 150 | 117 | 267 | 65.8 |
| | 80-84 | 100 | 94 | 194 | 62.8 |
| | 85+ | 102 | 69 | 171 | 65.8 |
| Total | | 493 | 449 | 942 | 64.8 |
| 2. Present W3 only | 70-74 | 13 | 11 | 24 | 5.0 |
| | 75-79 | 12 | 15 | 27 | 6.7 |
| | 80-84 | 16 | 12 | 28 | 9.1 |
| | 85+ | 12 | 10 | 22 | 8.5 |
| Total | | 53 | 48 | 101 | 7.0 |
| 3. Present W1 only | 70-74 | 19 | 31 | 50 | 10.5 |
| | 75-79 | 17 | 17 | 34 | 8.4 |
| | 80-84 | 20 | 19 | 30 | 12.6 |
| | 85+ | 16 | 13 | 29 | 11.2 |
| Total | | 72 | 80 | 152 | 10.5 |
| 4. Present W1, W3 | 70-74 | 54 | 40 | 94 | 19.7 |
| | 75-79 | 44 | 34 | 78 | 19.2 |
| | 80-84 | 27 | 21 | 48 | 15.5 |
| | 85+ | 15 | 23 | 38 | 14.6 |
| Total | | 140 | 118 | 258 | 17.8 |

some analyses of covariance, age at Wave 1 was included as a continuous variable. All analyses were carried out using SPSS for Windows, Version 8 (SPSS Inc, 1997).

Tinnitus status by age and sex

Participants were grouped according to the presence or absence of tinnitus at the two waves. This yielded four groups: Group 1 with no tinnitus at Waves 1 or 3 ($n = 942$, 64.8%), Group 2 with tinnitus at Wave 3 only ($n = 101$, 7.0%), Group 3 with tinnitus at Wave 1 only ($n = 152$, 10.5%), and Group 4 with tinnitus at Waves 1 and 3 ($n = 258$, 17.8%). Table 1 shows that the percentages of participants for both males and females, in each of the four tinnitus groups were roughly equivalent for each age group. That is, there was no relationship between tinnitus status and either sex or age group, and no interaction between tinnitus status, sex and age group.

Tinnitus and measured hearing

The relationship between tinnitus status and measured hearing was analysed using repeated measures analyses of variance (ANOVA), with either BEPTA or WEPTA as the dependent variable, Tinnitus Status (four levels) as the between subjects variable, and Wave (two levels) as the within subjects factor. Adoption of this strategy allowed identification of the effect on measured hearing of the passage of time, as well as that of the presence or absence of tinnitus at each wave. As age was substantially correlated with measured hearing level (around 0.46), each ANOVA was conducted twice. In the first, age was excluded from analyses so as to allow for post hoc comparisons at each wave, and in the second,

age at Wave 1 was included as a covariate, both to identify its effect and to identify the effects of the other variables after age had been adjusted.

Better ear pure tone average (BEPTA)

Table 2 shows the BEPTA means and standard deviations at both waves for each tinnitus group. When age was excluded from analyses, only one group difference emerged. Post hoc comparisons at each wave revealed that Group 4 had a higher BEPTA than Group 1 at Wave 3, (mean difference = 2.38 dBHL, $p < 0.05$). That is, participants with tinnitus at both waves evinced poorer measured hearing at Wave 3 than did those with no tinnitus at either wave. There were no other group differences at either Wave 1 or Wave 3, no differences among groups in BEPTA levels across the two waves and no interaction effects between Group and Wave.

Across all four tinnitus groups, there was an overall increase in BEPTA of about 2 dBHL from Wave 1 to Wave 3, $F(1,842) = 48.61$, $p < 0.001$. As shown in Table 2, the increase across waves for Group 4 was slightly, though not significantly, higher than for the other three groups.

Table 2 BEPTA by tinnitus status and wave

| Tinnitus Group | BEPTA | | | | N |
|--------------------|--------|-------|--------|-------|-----|
| | Wave 1 | | Wave 3 | | |
| | Mean | SD | Mean | SD | |
| 1. Absent W1, W3 | 29.48 | 12.09 | 31.67 | 12.55 | 565 |
| 2. Present W3 only | 32.39 | 11.50 | 33.71 | 12.60 | 58 |
| 3. Present W1 only | 30.66 | 10.43 | 32.5 | 11.68 | 74 |
| 4. Present W1, W3 | 30.94 | 10.92 | 34.05 | 11.91 | 149 |
| Total | 30.04 | 11.73 | 32.30 | 12.39 | 846 |

Age accounted for 19.5% of the variance in BEPTA across the two waves. Thus, as age increased, BEPTA also increased. After adjusting for age there was a significant difference favouring Group 1 over Group 4 in BEPTA across the two waves, (Group 1 < Group 4, mean difference 3.22 dBHL, $p < 0.05$).

Worse ear pure tone average (WEPTA)

Table 3 shows the means and standard deviations for the WEPTA at both waves. Worse ear pure tone averages exhibited more group differences than did BEPTAs. Without controlling for age, post hoc tests indicated that Group 4 had a higher WEPTA than Group 1 at both Waves 1 and 3 (respective mean differences = 3.70 dBHL and 4.44 dBHL), as well as a higher WEPTA across the two waves, $F(3,801) = 4.80$, mean difference = 4.07, $p < 0.01$. As with BEPTA, there was a main effect for Wave, with an average deterioration of around 2 dBHL across all groups, $F(1,801) = 39.62$, $p < 0.001$. Once again, there was a nonsignificant trend towards a greater difference between waves for Group 4.

As with BEPTA, age was substantially, though somewhat less, correlated with WEPTA, accounting for 15.9% of the variance across the two waves. As age increased, WEPTA deteriorated. Inclusion of age as a covariate in the analyses produced another difference amongst tinnitus groups: Group 1 had a lower WEPTA across the two waves than both Group 3 (mean difference = 3.56 dBHL, $p < 0.05$) and Group 4 (mean difference = 5.28 dBHL, $p < 0.05$).

Table 3 WEPTA by tinnitus status and wave

| Tinnitus Group | WEPTA | | | | N |
|--------------------|--------|-------|--------|-------|-----|
| | Wave 1 | | Wave 3 | | |
| | Mean | SD | Mean | SD | |
| 1. Absent W1, W3 | 35.49 | 12.87 | 37.87 | 13.98 | 540 |
| 2. Present W3 only | 39.01 | 12.64 | 41.02 | 12.83 | 55 |
| 3. Present W1 only | 38.34 | 12.81 | 40.82 | 13.92 | 73 |
| 4. Present W1, W3 | 39.19 | 12.56 | 42.32 | 14.86 | 137 |
| Total | 36.62 | 12.87 | 39.11 | 14.08 | 805 |

Table 4 Numbers and percentages of respondents with self-reported hearing difficulties by tinnitus status

| Variable | Tinnitus Group | | | | | | Total N |
|-------------------------------------|------------------|-------------------|-------------------|--------|---------|-------|---------|
| | 1. Absent W1, W3 | | 4. Present W1, W3 | | Gp1+Gp4 | Total | |
| | n | %Gp 1 | n | % Gp 4 | | | |
| Difficulty hearing background noise | 432 | 45.9 | 158 | 61.2** | 590 | 49.2 | 1200 |
| Difficulty hearing in quiet room | 97 | 10.3 | 51 | 19.8** | 148 | 12.3 | 1199 |
| Ever used hearing aid | 195 | 20.7 | 67 | 26.0 | 262 | 21.8 | 1200 |
| Use hearing aid now | 142 | 72.8 ^a | 48 | 71.6 | 190 | 72.5 | 262 |
| Consulted doctor hearing | 263 | 28.0 | 126 | 48.8** | 389 | 32.5 | 1198 |
| Consulted doctor tinnitus | 21 | 2.0 | 136 | 52.9** | 157 | 13.1 | 1197 |
| Visited hospital hearing | 41 | 4.4 | 31 | 12.1** | 72 | 6.0 | 1197 |
| Visited hospital tinnitus | 2 | 0.2 | 24 | 9.3** | 26 | 2.2 | 1197 |
| Visited NAL | 158 | 16.8 | 63 | 24.4* | 221 | 18.4 | 1198 |

^a= percentage of respondents who use hearing aid now (n = 262).

* $p < 0.01$; ** $p < 0.001$.

Self-reported hearing at wave 1

For ease of interpretation only Groups 1 (tinnitus absent at Waves 1 and 3) and 4 (tinnitus present at Waves 1 and 3) were considered during analyses of self-reported hearing difficulties. Table 4 shows the numbers and percentages of individuals in the two groups reporting each type of auditory difficulty. To determine whether or not there was any relationship between tinnitus status and self-reported auditory problems, chi-squares (Fisher's exact test, 2-sided) were computed. This allowed identification of any significant differences between the two tinnitus groups in percentages of respondents reporting a particular difficulty. For all variables except hearing aid use now or ever, a higher percentage of respondents in Group 4 than in Group 1 reported some degree of difficulty.

Non-auditory characteristics

As age was not substantially correlated with any of the variables constituting non-auditory characteristics, it was not included in any of the following analyses of variance. The tables related to the non-auditory items are available from the authors.

Depression

Complete data on depression at both waves were available for 1306 participants. The means for the entire group were 7.46 (SD = 6.69) at Wave 1 and 8.08 at Wave 3 (SD = 7.11), indicating that overall levels of depressive symptomatology were well below the criterion for possible depression. Repeated measures ANOVAs revealed a significant difference amongst groups in depression scores across the two waves, $F(3,1302) = 8.5$, $p < 0.001$. Pairwise comparisons showed that the mean for Group 1 was significantly lower than that of every other group, while the mean of Group 3 was lower than that of Group 2 ($p < 0.05$ in all cases). In addition, across all groups there was a significant, though small increase in depression from Wave 1 to Wave 3, $F(1,1302) = 4.86$, $p < 0.05$.

Post hoc comparisons showed that at Wave 1 the

mean for Group 1 (6.80) was significantly lower than those for Group 2 (9.55) and Group 4 (8.85), while at Wave 3, Groups 1 and 4 were not significantly different from each other, but were both lower than Group 2. An intriguing finding is that at both Wave 1 and Wave 3, the mean level of depression for Group 2 (those with tinnitus at Wave 3 only) is higher than that of all other groups, including those with tinnitus at both Waves.

Self-rated health

The mean ratings for self-reported health were 2.81 ($SD = 1.06$) and 2.98 ($SD = 1.06$) at Waves 1 and 3 respectively. Thus, as a whole the group rated their health as just above good. For self-rated health across the two waves there was a main effect for tinnitus group, $F(3,1448) = 5.19$, $p < 0.001$, with Group 1 reporting better health than Group 2 and Group 4, ($p < 0.05$) in both cases. There was an overall effect of wave, $F(1,1448) = 22.47$, $p < 0.001$, with an overall deterioration in health across all four groups of around 0.17.

Post hoc comparisons showed that at Wave 1, Group 1 reported better health than did Groups 2 and 4, while at Wave 3, Group 1 reported better health than did Group 2 only. Group 2 reported the worst health at both waves, following a similar pattern to that for depression.

Sleeping difficulties

Complete data for self-reported sleeping difficulties (trouble sleeping, waking at night, and waking early) were available for 1439 respondents. Overall, respondents experienced difficulty in these three areas at an average of "rarely" to "sometimes."

Across the two waves, tinnitus status exerted a significant effect on trouble falling asleep, $F(3,1435) = 11.51$, $p < 0.001$ and on early wakening, $F(3,1435) = 7.23$, $p < 0.001$, while for waking at night the effect just failed to reach significance ($p = 0.052$). The results for pairwise comparisons across waves were as follows. Groups 1 and 2 reported less difficulty falling asleep than did Group 4, while Group 1 also reported less difficulty than did Group 3 ($p < 0.05$). For both waking at night and early wakening Group 1 reported less difficulty than Groups 2 and 4 ($p < 0.05$).

Post hoc comparisons: Wave 1. Group 1 had less difficulty falling asleep than Groups 3 and 4 and Group 4 had less difficulty than Group 2. For waking at night here were no group differences, while for early wakening, Group 1 reported less difficulty than all other groups.

Post hoc comparisons: Wave 3. Group 1 reported less difficulty falling asleep and less early wakening than did Group 4, and less trouble with waking at night than did Group 2.

Discussion

Overall, older people with tinnitus perform more poorly on tests of measured hearing, and appear to

experience a lower quality of life in several domains than older people who do not report tinnitus. Group 2 (those reporting tinnitus at Wave 3 only) appears to stand out in terms of depression, self-rated health and possibly other variables. While recent onset of tinnitus might be expected to exacerbate quality of life, Group 2 appeared to be constitutively more depressed and report poorer self-rated health. Other explanations for the poorer quality of life in Group 2 may include stressors, such as bereavement, which may have been a tinnitus precipitator [12] or a more general response bias [13]. Further examination of existing data will enable the presence of stressors to be identified and the participants will also be tracked longitudinally.

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Tinnitus in the Federal Republic of Germany: A representative epidemiological study

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The object of epidemiological study on tinnitus in Germany was to evaluate the prevalence and the incidence rate of the symptom. In a random sample of persons aged more than ten years, 3049 telephone interviews were performed. The sample was stratified by the state in order to realise an exhaustive reflection of the country.

The main results with high representativity:

18,7 million citizens (24,9% of population) have or have once head noise in the ear.

2,9 million citizens (3,9% of population) had noise in the ear at time of the study.

2,7 million citizens (3,6% of population) have ear noise lasting longer than one month.

Each year there are 250.000 citizens (0,33% of population) as new chronic patients.

53% of patients with chronic tinnitus report a hearing impairment but only 7,5% of these patients have been supplied with a hearing aid.

13% of patients regard the medical assistance as very helpful, 20% as completely inadequate.

55% of patients replied that no therapy had helped, 93% reported that most damage had been done through no therapy having been performed.

Introduction

There has so far been no study conducted of the incidence and prevalence of tinnitus in the Federal Republic of Germany.

The estimates given in the medical literature over the past few years are based on the one hand on a study conducted by the Grünes Kreuz (*Green Cross*) in 1985 (1) into the hearing ability of the Germans and a regional study in the Württemberg region (2) and, on the other hand, on the transposition of statistical data from other countries (e.g. Great Britain (3, 4), Sweden (5), France (6)) to the population of the Federal Republic of Germany.

On the basis of these estimates, it was assumed in the past that there are some 8 to 10 million people in Germany who suffer from chronic tinnitus and 10% of these (0.8 to 1 million) experience great suffering and are in need of therapy.

Over the past few years, the "tinnitus problem" has been receiving increasing coverage in the popular press. Figures ranging from 2 million to 25 million tinnitus patients have been reported, causing great unease amongst patients at times.

The German Tinnitus League has thus long felt the need for a study to be carried out in order to make reliable figures available for the Federal Republic of Germany.

In the past, this project has always failed to materialise due to a lack of funding, since no money was available from the public purse.

Only when an appeal for donations was launched among League members did it prove possible to raise a sum of more than DM 100,000 within a short period of time, and to win the Audiological Technology Division of Siemens as a sponsor for the remaining costs.

Questions

An answer was to be found to the following questions:

- 1) How many citizens of the Federal Republic of Germany are familiar with the symptom of tinnitus through having experienced it themselves?
- 2) How many citizens of the Federal Republic suffer from chronic tinnitus?
- 3) Is there an age, sex, occupational, or geographic-specific distribution?
- 4) What is the level of suffering caused by chronic noise in the ear?

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- 5) How many new cases of tinnitus must be expected each year?
- 6) Is it possible to draw a time limit between acute and chronic tinnitus?
- 7) What is the situation regarding medical care, how is this rated by the patient?
- 8) What influence does tinnitus have on lost working hours, curtailing the ability to work and employees being sent into early retirement?

Method

In order to obtain a representative sample of citizens of the Federal Republic of Germany and to question them in an efficient manner, the telephone interview was selected as a survey method, within the framework of an open study. A six-page questionnaire (45 questions) was worked out on the basis of the questions set out above, without any open questions as far as possible.

In order to come as close as possible to representativity, the method of three-stage stratified random selection was employed:

- 1st stratification: selection of the Federal state, interview frequency per number of inhabitants
- 2nd stratification: selection of households, each private household with a telephone must have the same selection probability. (Elimination of business lines).
- 3rd stratification: selection of the target person in a household through the "date-of-birth method".

The interviews were conducted by trained staff at the Institut für empirische Gesundheitsökonomie (*Institute of Empirical Health Economics*).

An overall random sample of 10 000 persons was taken. Through "eliminations of the first kind" (telephone line does not exist, not a private line, target person unable to follow the interview, place of residence outside Germany) an adjusted random sample of 7409 persons was obtained.

Eliminations of the second kind (target person unattainable three times running, refusal to participate, interview broken off prematurely), the actual random sample was 3049 persons, giving an exhaustion level of 41.2%.

For purposes of achieving a high representativity in the Federal Republic of Germany, it is necessary to interview 3000 people. This condition was fulfilled.

The interviews were conducted over the period December 1998 to February 1999, on a daily basis between 15.00 and 20.00. Children below the age of 10 were excluded.

Results

The main results of the studies with a high representativity will be presented in what follows:

- 1 18.7 million citizens aged over ten (24.9% of the population) have or have once had noise in the ear.
- 2 9.8 million citizens aged over ten (13% of the population) have or have once had noise in the ear lasting longer than 5 minutes.
- 3 2.9 million citizens aged over ten (3.9% of the population) had noise in the ear at the time of the study.
- 4 2.7 million citizens aged over ten (92% of 3 above) have ear noise lasting longer than one month.
- 5 1.5 million citizens aged over ten (approximately 50% of 3 above) consider the effect of their ear noise on themselves to be between moderately serious and unbearable.
- 6 Each year there are 0.25 million citizens aged over ten (0.33% of the population) as new chronic tinnitus patients after subtraction of the mean mortality rate and the therapy success rate.
- 7 The prevalence of tinnitus within the individual federal states is between 1% and 2% (Saarland, Thuringia, Saxony) and 6% to 8% (Hesse, Baden-Württemberg, Bremen). If the prevalence of tinnitus is worked out on the basis of North/West/East and South Germany, then the order is as follows: East (2.7%), West (4.0%), North (5.2%), South (6.0%).
If the prevalence of tinnitus is calculated according to age and region, and the old federal states compared with the new ones, then the new federal states are in the lead for the 40 to 60 year-olds. For young people and old people, the Western states are in the lead by a long way.
- 8 The prevalence of tinnitus according to sex shows a minimally higher level for men but this is not significant.
The prevalence of tinnitus according to age shows a pronounced increase between the 50th and 80th year of age.
The prevalence of tinnitus according to occupation shows a much greater incidence in those who are not in work. It would, however, be logical to assume that this big influence does not really exist, since virtually the entire group of over-sixty-year-olds (this group displays high prevalence figures) is not in work.
- 9 If a dividing criterion of 1, 2 and 3 months is placed between acute and chronic tinnitus, then this is seen to be unnecessary, since only 1.03 times more chronic cases are registered after three months than after one month.
- 10 When questioned about their subjective reasons for the development of tinnitus, then medical grounds are given as the reason in 36% of cases, stress in 25% of cases and noise at the workplace in 17% of cases.
- 11 When asked about the nature of the stress-conditioned triggers, stress at work was cited in 54% of cases and family stress in 21%.
- 12 46% of those questioned report a gradual increase in the disturbance caused by tinnitus. 43% report a sudden onset with stagnation.

- 13 19% of those interviewed indicated that the noise became constantly stronger. 8% had the impression that it became weaker and 50% that it remained the same, while 23% had a fluctuating impression.
- 14 38% of those questioned experience the noise on the left, 39% in the middle, or in both ears, and 22% on the right.
- 15 53% report a high-frequency whistling, 35% a medium-frequency noise and 8% a low-frequency hum.
- 16 37% only hear the noise in their ears during silence, 44% with a low level of ambient noise and, in 17% of cases, the ear noise drowns all ambient noise.
- 17 36% feel themselves most impeded by the noise at home, 16% at work and 26% during their leisure time.
- 18 5% frequently experience anxiety concerning their ear noise, 4% very frequently and 1% continuously.
- 19 6% report a single or repeated instances of absence from work on account of their ear noise.
- 20 53% report a hearing impairment in the affected ear(s).
- 21 7.5% of the test persons under 20 above have been supplied with a hearing aid.
- 22 44% of chronic tinnitus sufferers report sensitivity to noise at the same time (hyperacusis).
- 23 81% of chronic tinnitus sufferers have consulted one or more doctors on account of their ear noise – 56% of these on a permanent basis. In 89% of cases, ENT doctors are consulted.
- 24 13% of patients regard the medical assistance as very helpful, 24% as helpful, 23% as not very helpful, 18% as inadequate and 20% as completely inadequate.
- 25 A therapy was conducted for 52% of the patients who consulted medical assistance. In 73% of these cases, this was outpatient therapy, and in 29% of the cases inpatient therapy. (Multiple answers possible.)
- 26 When questioned about the type of outpatient therapy, 75% specify medicamentous therapy, followed by a very large number of other therapy methods (e.g. 9% radiation, 7% iontophoresis, 6% ozone therapy, 4% maskers, 4% pressure chamber, 2% outpatient psychological therapy, etc.).
- 27 When asked which therapy helped most, 55% of those concerned replied that no therapy had helped.
- When asked which therapy did the most damage, 93% reported that most damage had been done through no therapy having been performed.
- 28 16% of patients said that they treated their ear noise themselves, 29% by listening to music, 29% through hearing protection, 14% with homeopathic remedies.
- 29 4% of those concerned have taken early retirement on account of the ear noise.
- 30 11% of these patients qualify as having a disablement, with this being attributable solely to the ear noise for 29% of these patients.

Discussion

What use are these figures to us?

- 1) In the context of this study, representative data was obtained on the point prevalence and incidence of tinnitus for the Federal Republic of Germany. The point prevalence for acute and chronic tinnitus is 3.9%, which means that, at the time of the study, 2.9 million federal citizens were affected by tinnitus. This is a relatively high figure compared with other "national diseases". A prevalence of 4–5% is described for diabetes mellitus for Germany, and 15% for arterial hypertension (7).
- 2) The figure of 1.5 million affected from a moderate to a very severe level is greater than previously assumed.
- 3) 340 000 (adjusted to 250 000 after allowance for the death rate and therapy success) new cases of chronic tinnitus per year constitute a medical challenge, although they may also call for a socio-political rethink.
- 4) In respect of the age distribution, the age groups between the 60th and 79th year were the years that were most affected. The different age peak in the new federal states is very interesting and can be interpreted in many different ways.
- 5) The tiresome discussion about acute and chronic tinnitus (this discussion is virtually only pursued in Germany by providers of acute therapy) can probably very soon stop for good.

With a high level of probability, a continuously persistent ear noise can be regarded as chronic after just a few weeks.

- 6) Many tinnitus patients suffer impaired hearing at the same time. The provision of hearing aids still leaves a great deal to be desired.
- 7) More than 60% of those affected regard the medical assistance provided as being either of little help, inadequate or completely inadequate. This doubtless constitutes a reason for a further focus in training. On the other hand, 37% of those affected rate medical assistance as helpful to very helpful. This major disparity in the assessment of the work of the medical profession points to the different attitudes held by the medical profession to the symptom of tinnitus.
- 8) There will never be a uniform therapy concept for a chronic symptom. It would, however, be desirable to see an end to the current polypragmasy.

Are the results that have been obtained really of any value?

Is it possible, from 3049 interviews conducted, with 135 telephone partners having chronic tinnitus, to draw conclusions about the population as a whole?

Drawing a conclusion from the composition of the random sample regarding the composition of the population is permissible with a representative sample and is called an "inductive conclusion" [8,9,10]. This exploits the fact that the characteristics surveyed occur in roughly the same distribu-

tion in the parent population as in the random sample.

The number of people affected by tinnitus in Germany is thus to be regarded as a significant result on the basis of statistical criteria.

The bigger the random sample selected, the more accurate the statement will be (Law of large numbers). The standard deviation of our estimate can be precisely calculated on account of the random selection; for the case number of 3049 it is 0.35%.

The statements on the subgroups are, naturally, less accurate, but they are still representative, since the target persons were selected on a representative basis.

A discussion of the results for the Federal Republic of Germany and the epidemiological results for other European countries since 1981 is particularly difficult, since the interview methods and questions, and also the number of test persons differ a great deal. The results can be compared relatively well with the results for England, however.

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Deep brain stimulation effects on hearing function and tinnitus

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Current models and evidence suggest that chronic tinnitus is mediated by central and sometimes non-auditory brain structures. New treatment strategies, based upon a model of central tinnitus mediation, must be developed. It has been recently proposed [1] that electrical stimulation of deep brain structures should have the potential of providing tinnitus relief. Deep brain stimulation (DBS) has been applied, with reasonable success for relief from tremor and chronic pain. Stimulation for movement disorders is typically presented to the medial nucleus of the thalamus or the globus pallidus, or subthalamic nucleus, contralateral to the affected side. Stimulation for chronic pain has been most commonly applied to the peri-ventricular/peri-aqueductal gray matter of the mesencephalic/diencephalic transition area. Stimulation of thalamic auditory structures may provide relief from tinnitus by disrupting reverberant abnormal activity within auditory nuclei.

The purpose of this study was to determine if DBS could possible provide tinnitus relief as well.

Questionnaires were mailed to 30 patients who had received DBS for movement disorders including Parkinson's disease and essential tremor. Twenty-nine responses were returned. The questionnaires included questions regarding hearing problems, tinnitus and whether or not DBS had any effects on either. Although 8 patients reported hearing problems, none reported any change in hearing related to DBS. All hearing difficulties existed prior to DBS implantation. Seven patients reported having tinnitus. Four of the seven reported that the stimulation did not affect their tinnitus in any way. The remaining three all reported that the loudness of their tinnitus was lower when their stimulators were activated than when they were turned off.

All seven of the subjects with tinnitus were requested to participate in extensive follow-up evaluations. To date, four have received audiometric evaluation, tinnitus characterization, and test-retest evaluation with the DBS units turned on, then off, then on again. Two of the returning patients had reported by questionnaire that their tinnitus was unaffected by DBS. That proved consistent with our testing under controlled conditions in the clinic. Two reported by questionnaire that her tinnitus was quieter when their stimulators were activated. This also proved true during evaluations.

These results support the idea that tinnitus may be enhanced or perpetuated by non-auditory structures. It is possible, but unlikely, that current had spread from the stimulating electrodes to auditory regions of the brain. The study does indicate that DBS provides tinnitus relief for some and is a technique worthy of future study.

Introduction

Tinnitus is an auditory phenomenon occurring in a significant number of people. Estimates range from 13 to 18.6% of the general population experience problematic tinnitus. The variation of estimates is most likely due to the way in which the data were acquired. Regardless, the number in the United States alone appears to be upwards of 40 million

people. Of those, approximately 10 million experience it to such severity that they seek medical attention and 2.5 million are considered disabled by it. The United States Veterans Administration will pay 120 million dollars this year in disability benefits due to tinnitus.

Tinnitus is almost universally experienced in some form [2]. Most cases resolve spontaneously. Recovery may occur in seconds, hours or days. Some forms of objective tinnitus, related to mechanical factors, can be treated surgically or medically. Even subjective tinnitus related to tumors of the auditory nerve or disease processes of the middle ear may be relieved by medical intervention. How-

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ever, there are numerous cases that do not dissipate. Clinical experience indicates that the likelihood of tinnitus resolving is extremely small as it has been present for six months to a year or longer. To date, there is no cure for chronic tinnitus.

Existing treatments: acoustic therapy

Treatment and management of chronic tinnitus has become increasingly successful. Acoustic therapies employ the use of sound to treat the tinnitus patient. Sound may be used to provide immediate relief and/or to facilitate long-term changes in the auditory neural system influencing the perception of tinnitus.

Masking can provide immediate relief by using competing sound to either reduce or eliminate perception of the tinnitus [3]. Masking may result from a number of sources. Ear level maskers or noise generators provide continual background sound that may be controlled by the user. Hearing aids (when warranted by the presence of a hearing loss) may amplify background environmental sounds to levels that provide adequate distraction for the patient. Some ear-level units combine amplification and noise generation capabilities to further meet the needs of those with hearing loss and tinnitus. External devices and recordings are available that generate environmental type sounds and bands of noise which diminish the perception of tinnitus for many. Ultrasonic bone conduction oscillation using a sweep frequency stimulus increased the duration of residual inhibition in a pilot population, but the typical duration of relief remains on the order of a few minutes [4].

It has been postulated that exposure to continual, low-level, broad-band sound will take advantage of neuronal plasticity and facilitate habituation to the tinnitus signal. This is a long-term process that may take up to two or more years to complete [5]. The strategy is based upon the idea that sub-cortical and cortical centers along the auditory pathway are critically involved in the detection and perception of tinnitus. It also postulates that non-auditory structures such as those found in the limbic system are critically involved in the perpetuation and enhancement of tinnitus through emotional linking of significance to the tinnitus signal. Functional imaging studies have provided evidence for central neural activity related to tinnitus [6–8]. Education and counseling regarding the nature of the individual's hearing health, tinnitus, and tinnitus mechanisms, as well as validation and reassurance are critical components of "retraining" strategies.

Individuals with profound hearing loss are difficult to manage with acoustic therapy. There are severe limitations on using the auditory system to either provide immediate relief or long-term stimulation. Reports contend that up to 93% of cochlear implant recipients found some relief from their tinnitus [9]. Ultrasonic bone conduction stimulation has provided hearing for the profoundly hearing impaired but has not yet been evaluated in that population for providing tinnitus relief.

Existing therapy: medications

In parallel to acoustic therapy, several drugs have been used to provide tinnitus relief [10]. Most reports using medications are either anecdotal or poorly controlled. However, there are some medications that have been reasonably evaluated and appear to be effective. Alprazolam (Xanax) is a benzodiazepine developed as an anti-anxiety treatment [11]. In relatively high doses, it reduced both the objectively matched and subjectively scaled measures of tinnitus loudness. Nortriptyline is a tricyclic medication developed to treat depression. It was shown to assist depression and reduce the matched tinnitus loudness [12]. It is likely that other neuronal function modifying medications in the benzodiazepine and tricyclic families will prove to be useful for some tinnitus patients. It is also possible that serotonin specific reuptake inhibitor medications may also provide relief for some. Carefully controlled studies using pre-selected subject populations with well-defined tinnitus profiles must be performed to determine the ultimate utility of these medications.

When appropriately applied, acoustic therapy, counseling/education, and medications in a combination specifically selected for an individual's personal profile and needs, tinnitus relief is often provided. However, there are a significant number of tinnitus patients who come into the clinic for whom we can not provide adequate relief. The individuals become increasingly despondent, depressed and desperate. It is disturbing to have a patient plead for any procedure that will provide relief – even to the point of asking to be deafened rather than to go on with tinnitus. Unfortunately, experience with auditory neurectomy for tinnitus relief has been less than encouraging. Patient often wake up with only tinnitus and that often exacerbated compared to the pre-operative condition.

Proposed therapy: deep brain stimulation

It has been suggested elsewhere in this text [1] that stimulation of deep brain structures should be able to disrupt abnormal neural firing patterns that perpetuate and enhance the perception of tinnitus. Deep brain stimulation (DBS) has been used to treat movement disorders related to Parkinson's Disease and essential tremor. It has also been used to provide relief for chronic pain. Shi and Martin [1] have developed a model in which stimulation of auditory centers at the level of the thalamus should provide relief from tinnitus in ways similar to relief from tremor and chronic pain. The suggested thalamic stimulation region that should provide relief is the ventral division of the medial geniculate body. This division is arranged tonotopically and relays the majority of auditory signals from the brainstem to the primary auditory cortices. Interestingly, Jeanmonod, et al. [13] noted that medial thalamotomy produces relief from a wide range of neurological symptoms in a population of 104 patients including neurogenic pain, movement disorders,

epilepsy, neuropsychiatric disorders and tinnitus. Six of the patients had tinnitus. Three of the six reported improvements following medial thalamotomy, however, details of the patients' hearing and tinnitus history, function and measurements were not reported. The most notable result was that one patient had complete relief from tinnitus following the procedure.

Even though there is reasonable theoretical basis to support DBS for treating tinnitus, the risks of performing a neurosurgical procedure preclude further experimentation without supporting evidence that this technique will be profitable. The purpose of this study was to determine if supporting evidence could be obtained that would support the application of Deep Brain Stimulation for the treatment of severe chronic tinnitus. A questionnaire was sent to patients receiving thalamic DBS implants asking them about the influence of stimulation on their tinnitus and hearing. We recognized that the thalamus is not an auditory structure, but ablation studies had indicated that it might be involved in the perception of tinnitus [13].

Methods

Thirty patients were implanted with unilateral or bilateral deep brain stimulation electrodes to treat the movement disorders related to Parkinson's disease or essential tremor. Simple screening questionnaires were mailed to those patients, asking them if they had tinnitus or hearing problems. Twenty-nine questionnaires were returned. Patients reported to have tinnitus were invited to our program for extensive follow-up evaluations. Patients that were willing to participate filled out extensive patient questionnaires, were interviewed, received full audiometric evaluations and tinnitus evaluations in a sound proof booth. Baseline testing was performed with DBS units on. Repeat testing was performed at least 20 minutes after the DBS units were turned off, and again after the units were reactivated. Comparisons were made between ON and OFF DBS conditions.

Results

Seven of the respondents claimed to have tinnitus. Three of the seven reported that their tinnitus was "quieter" when their stimulators were ON than when they were OFF. None of the seven reported changes in hearing related to stimulation. Two patients reporting no DBS related changes in their tinnitus and two reporting that their tinnitus decreased with DBS activity came to the clinic for testing. During follow-up testing, these patients were tested with their stimulators ON and OFF. Significant decreases in rated and matched tinnitus loudness were found in the two patients who had indicated that possibility by their responses to the questionnaire. The other two patients had no

significant changes. No changes in hearing thresholds were reported or measured. All four of the patients who came in for follow-up testing had received stimulating electrode implants in the ventralis intermedius (VIM) of the thalamus. This structure is targeted for providing relief from movement disorders.

A summary of results for each patient is presented:

Patient 1: An 84 y.o. woman who had been treated for essential tremor by receiving a left VIM thalamotomy in 1994 that was revised in 1998. She received a DBS implant in the right VIM in 1998. She had a bilateral, mild-severe high-frequency sensory neural hearing loss. She first noted a hearing loss about nine years ago. She had bilateral hissing tinnitus that began 1-2 years ago. She reported that she thought her tinnitus was quieter when the stimulator was ON than when it was OFF.

On the day of her evaluation, she had no perception of tinnitus during baseline tests with the stimulator ON. This was not her normal condition and she reported that her tinnitus usually lasted for several hours at a time. Immediately after her stimulator was turned OFF, she still could not hear any tinnitus. After 15 minutes, she reported tinnitus that was matched to a 2 kHz tone bilaterally with a loudness rating of 5 of 10 and a loudness match of 6 dB SL on the right and 3 dB SL on the left. Within 6 minutes of turning her stimulator ON again, she could no longer hear her tinnitus (Note: That was the time it took to transport her from the DBS control system to the sound booth. Subjectively, she received immediate tinnitus relief)

Patient 2: A 71 y.o. man who had been treated for essential tremor by receiving bilateral VIM DBS implants in 1997. He had a bilateral severe sensory neural hearing loss that he had been aware of since 1950. His tinnitus was a continuous hum that filled the head that began more than 20 years ago. He did not think that his tinnitus was affected by DBS activation.

During baseline testing with the stimulator ON, he matched his tinnitus to a 250 Hz tone at an average 1.75 dB SL (repeated tests) with a loudness rating of 7 of 10. After the stimulator had been OFF for over 35 minutes, he had a loudness match of 1.5 dB SL. When the stimulator had been turned ON again, his loudness match remained at 1.5 dB SL.

Patient 3: A 65 y.o. man who had been treated for essential tremor by receiving a right VIM DBS implant in 1997. He had a long standing, bilateral, mild-severe high-frequency sensory neural hearing loss. He had bilateral ringing tinnitus, worse on the right, which had begun more than 20 years ago. He did not think that his tinnitus was affected by DBS activation.

During baseline testing with the stimulator ON, he matched to at 6 kHz tone at an average of 3 dB SL and rated the loudness as 3 of 10. After the stimulator had been off for over 40 minutes, he rated the loudness at 3 of 10 and loudness matched his tinnitus at 5.8 dB SL. When the stimulator had been turned on again, his loudness rating remained

3 of 10 and the loudness match was 5 dB SL. Although there was an initial increase in his matched tinnitus when the stimulator was turned from ON to OFF, it did not decrease enough to be considered a significant change when the stimulator was turned ON again.

Patient 4: A 69 y.o. woman who had been treated for essential tremor with right VIM thalamotomies in 1997 and 1998, and by a left VIM DBS implant in 1998. She had a bilateral mild, high-frequency hearing loss. She had bilateral ringing tinnitus, louder on the left, which began 6–10 years ago.

During baseline testing with the stimulator ON, she matched to a 750 Hz tone with a loudness rating of 5 of 10 and a loudness match of 15.3 dB SL. After the stimulator had been turned OFF for 20 minutes, she had a loudness rating of 6–7 of 10 and a loudness match of 35.6 dB SL. When the stimulator was turned off, she had a loudness rating of 4 of 10 and a loudness match of 17.8 dB SL.

Discussion

The results of this study support the observations of Jeanmonod *et al.* (1996) that the thalamus may be involved in the perception of tinnitus. The absence of any effect of DBS on hearing in the presence of stimulus related changes in tinnitus supports the hypothesis that non-auditory structures may be involved in the enhancement or perpetuation of tinnitus.

Why did thalamic stimulation reduce or eliminate tinnitus?

1. The thalamus is an incredibly complex relay center with ascending and descending motor and sensory connections. Jeanmonod *et al.* [13] found that several chronic neurologic symptoms (including neurogenic pain, abnormal movements, certain neuropsychiatric disorders and tinnitus) were related to thalamic single-unit activity that met the extracellular criteria of low-threshold spike bursts. They concluded that all of the symptoms had a common feature centered on a “self-perpetuating thalamic cell membrane hyperpolarization similar to the one seen in slow-wave sleep.” Low-threshold spike bursts are initiated by the deactivation of calcium channels. A loss of afferent excitation or an increase in inhibition can result from membrane hyperpolarization and therefore positive symptoms may occur.

2. Current may have spread to auditory-related pathways or structures. During development of the model for DBS treatment of tinnitus [1] we had anticipated that auditory structures within the thalamus (medial geniculate) would need to be stimulated in order to alter tinnitus in any way. It is possible that there was a current path to the medial geniculate. This seems unlikely because subjects finding relief in the Jeanmonod *et al.* study had medial thalamic ablations in which current stimula-

tion was not used. In addition, current spread in thalamic stimulation often creates other unwanted movements and sensations that were not markedly present in these patients.

3. The patients had a placebo effect. We did not tell the patients to expect that their tinnitus would change for better or worse, or even at all. We only asked them to report any differences and to perform the matching tests. It is difficult to blind this type of study because there is often some somatic sensation related to when the DBS is activated.

Why did thalamic stimulation *not* work for some patients?

1. Each individual having tinnitus represents a unique combination of heritage (genetics), global pathophysiology, and psychoperceptual factors. It is not likely that any treatment will provide relief for all tinnitus sufferers.

2. It is interesting that the two subjects in our study who did not respond had onset of their tinnitus and hearing losses over 20 years before our testing. The two subjects who did respond had tinnitus for either 1–2 or 6–10 years. It is possible that the factors related to tinnitus perception become less plastic over very long periods of time.

3. We have yet to determine the exact electrode location and stimulus characteristics that were or were not effective for tinnitus relief with DBS. It is not possible to move the electrodes once they are in place, but it is possible to vary stimulus intensities, rates and electrode configurations. It seems likely that stimulus characteristics would modify the effects of DBS on tinnitus.

Factors that did not seem to be of importance were tinnitus pitch, loudness match, loudness rating, audiometric configuration or speech discrimination or location of the DBS implant.

It was not surprising that 7 of 29 (24%) respondents reported having tinnitus. The majority of the DBS patients queried were elderly and the incidence of tinnitus is relatively high among seniors. It was interesting that 3 of 7 patients with tinnitus subjectively reported improvement with their DBS units activated. One of the three improved patients was lost to follow-up. The remaining two non-improved patients will be tested as soon as possible. It is also important to note that none of the 7 patients we contacted who had tinnitus considered it problematic enough to seek medical help.

These preliminary results are encouraging. When combined with the ablation data of Jeanmonod *et al.*, 6 of 13 (46%) patients obtained relief from thalamus treatments. Two of the 13 patients had total suppression of their tinnitus. The patients who found relief from DBS also had relatively prolonged periods of residual inhibition after their stimulators had been turned off. These studies suggest that it may soon be possible to offer alternative treatment options to tinnitus sufferers that have otherwise not been able to obtain relief.

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Local drug delivery systems for the treatment of tinnitus: Principles, surgical techniques and results

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Local treatment of inner ear diseases involves the direct application of pharmacological substances and/or electrical stimulation of the inner ear structures. In contrast to systemic pharmacotherapy, this presents no dosage problems, results in no systemic side-effects and bypasses the blood-cochlea barrier. The round window membrane is the preferred access.

The basic precondition is a stable coupling element, which allows a controlled drug release into the perilymphatic space. While technical difficulties do not allow direct access to the perilymphatic space, a catheter possessing a certain shape may be inserted into the round window niche. The double lumen flow system allows the variation of concentration and flow. This application system, including an external micropump, was tested in a prospective placebo-controlled clinical study involving 20 patients. The substances lidocaine, glutamate, glutamic acid, diethylester, caroverine and gentamycin were applied following implantation during tympanoscopy. An oto- and vestibulo-toxic effect was shown to be reliably achievable in Menière disease (MD) patients. Patients suffering from tinnitus reported a temporary suppression.

The results show that the drugs may be effectively released into the round window via the round window membrane, although the effect was produced only in some patients. In addition, owing to the differentiated effect of individual substances, conclusions could be drawn as to the pathophysiology of tinnitus. A long-term therapy in cases of tinnitus and sensorineural hearing loss, however, is only possible with totally implantable microdosage systems which have not, as yet, been developed.

Introduction

Local treatment of inner ear diseases has only occasionally been administered in the past. Extensive data is only available for intratympanic gentamycin therapy, which Lange [1] introduced to clinical practice more than 20 years ago and modified several times. Further experience has been gathered with the transtympanic application of lidocaine [2] and cortisone [3]. These attempts to treat tinnitus are based on the assumption that the intratympanically applied substances can come into contact with the round window membrane and permeate it by diffusion. Despite some conflicting data, the results achieved to date are promising.

The main advantages of local drug delivery systems for the treatment of tinnitus include the bypass of the blood-cochlea barrier, the lack of systemic side-effects, the wide dosage range, the

extensive range of substances and the potential use of electrostimulation.

Among the disadvantages are the necessity of a surgical procedure, local side-effects in the inner ear, only short-term benefits from treatment and the lack of coupling elements and implantable microdosage systems.

Access may also be gained through the stapes foot plate and the endolymphatic sac.

Several drug groups are available for the local treatment of inner ear diseases (Table 1).

Table 1 Drugs for local therapy

| | |
|---------------------------|---------------------------------|
| Membrane-effective drugs: | lidocaine, novocaine, phenytoin |
| Anti-inflammatory drugs: | corticosteroids |
| Transmitter (agonists): | glutamate |
| Transmitter antagonists: | GDEE, caroverine |
| Ototoxic drugs: | gentamycin, neomycin |

To control particular anatomical features such as pseudomembranes, adhesions and insufficient depth of the round window niche, which is essential for a targeted drug delivery into the inner ear, Arenberg 4 developed a double-tubed catheter with

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specially formed coupling elements to be inserted into the round window niche. The μ Cath system has perforations to bring the drug into direct contact with the round window membrane. The catheter may be fitted with an external micropump system.

To test the effectiveness of this application mode in cases of inner ear disease, the catheter was used in a prospective placebo-controlled study. The aim of the study was to answer the following questions:

- (1) Is local drug treatment feasible via the round window?
- (2) Which dysfunctions of the inner ear may be treated?

Patients and methods

The study included twenty patients suffering from inner ear disease. Five of them had Menière disease which was resistant to conventional treatment, while the other 15 patients had chronic tinnitus and sensorineural hearing loss. The patients were aged between 25 and 73 years. The duration of the disease ranged between 1 and 14 years.

During the prospective placebo-controlled study, the catheter was placed at the round window under local anaesthetic and several substances were applied for a period of several days. The catheter was then removed.

Surgical procedure

A tympanoscopy was performed under local anaesthetic, exposing the round window membrane. Scars or mucosal folds were removed. Bone spicules located in the hypotympanum were removed with a drill and an osseous canal was created for the catheter in the posterior inferior wall of the auditory canal. Then the diameter of the catheter was established and a catheter of appropriate size inserted. The catheter was guided in an external direction, the tympanomeatal flap was repositioned and the catheter secured with sutures at the superior wound edge. The catheter may be pulled out upon completion of the therapy.

MD patients were subjected to continuous daily application of 40 mg gentamycin. The therapy was terminated as soon as a nystagmus and/or a threshold decrease occurred (on average after 3–5 days). Tinnitus patients were treated in accordance with the tinnitus scheme displayed in Table 2.

Table 2 Tinnitus Scheme

| | |
|-----------------------------------|---------------------------|
| Lidocaine 2% in increasing dosage | (20–100 μ l per hour) |
| Glutamate | (0.5–2.5 mg per hour) |
| GDEE | (0.5–2.5 mg per hour) |
| Caroverine | (0.8–4 mg per hour) |
| Saline solution 0.9% | (20–100 μ l per hour) |

Saline solution was used as a placebo and was also applied over night following the delivery of the various drugs in order to wash out the substances. A record was kept of the results with each substance. The frequency of the vertigo attacks in MD patients and the loudness of the tinnitus ($\geq 50\%$) in tinnitus patients served as parameters. The minimum observation period was 6 months.

Results

MD Patients

The vertigo disappeared in 4 out of 5 patients and was considerably relieved in the other patient. The number of vertigo attacks was reduced by more than 50%. 3 out of 5 patients experienced additional hearing loss during the therapy, one patient suffering total hearing loss.

Tinnitus Patients

The tinnitus loudness was reduced by at least 50% with:

- lidocaine in 2 of 15 patients;
- glutamate in 3 of 15 patients;
- caroverine in 2 of 15 patients;
- saline solution in 1 of 15 patients.

The improvements were temporary and lasted in some cases for several days. The majority of patients experienced no change in their symptoms.

Discussion

The μ Cath system allows a targeted drug delivery in the area of the round window niche. During the delivery process, gentamycin diffuses reliably into the perilymphatic space, resulting in the disappearance of the vertigo symptoms in MD patients. However, as a side-effect the majority of patients experienced an additional hearing loss, indicating an ototoxic effect of gentamycin. The main advantage as compared to conventional transtympanic application is the controlled application of the drug at the round window niche. Externally invisible anatomical conditions in the middle ear often prevent gentamycin from coming into contact with the round window membrane or render the gentamycin delivery difficult to control. These include scars caused by previous inflammations, mucosal velums containing a pseudomembrane and swollen mucous membranes as a result of tympanic instillation or the insertion of grommets. The swelling may result in a total lack of effectiveness, as the increased blood flow in turn causes a higher rate of drug flow. During the tympanotomy, however, the round window membrane is reliably exposed and the catheter reliably positioned.

On the basis of the results presented in this paper, drug application is only effective in a limited number of cases of chronic tinnitus and sensorineural hearing loss. Two possible explanations are as follows:

- (1) On the one hand, the substances may not be able to permeate the round window membrane and reach the site of action in the inner ear in sufficient concentration. This hypothesis is contradicted by the observations of Sakata [2], who was able to achieve considerable cochleovestibular side-effects during local application of lidocaine in sufficient concentration, which may only be accounted for by the drug having permeated into the perilymphatic space. Side-effects of this kind were only observed in some of our patients, but this indicates a diffusion through the round window membrane.
- (2) The tinnitus-generating mechanisms are not located in the inner ear or the structures which may be accessed via the perilymphatic space. It is a widely held opinion that tinnitus is induced by false coding in the auditory system. This incorrect coding may be generated by various damaging mechanisms in the inner ear, leading to alterations in the stochastic spontaneous activity of the auditory nerve fibres. Different discharge patterns of individual auditory nerve fibres and abnormal synchronisation between individual auditory nerve fibres result in an information content which generates the sensation of tinnitus. This concept is validated by numerous experimental findings, leading to the assumption of a central genesis of tinnitus [5,6,7]. Previous experimental findings by one of the present authors point in the same direction [8]. This means that only individual cases of tinnitus are susceptible to local application of the substances used in this study. This is in contrast to the effectiveness of systemic application, which was also performed in some of the patients. However, no firm conclusions can be drawn as the data for some patients is insufficient.

Summary

Targeted local drug delivery for the treatment of inner ear diseases is possible with specially developed catheter systems. Further improvement may be achieved in the future with the development of special coupling elements which penetrate the round window membrane, the stapes foot plate or the endolymphatic sac and allow direct application in the perilymph and endolymph. An implantable microdosage system is needed to achieve long-term results, e.g. for genetic therapy and long-term tinnitus treatment.

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Validation of treatment outcome measures

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Tinnitus evaluation is essential especially when it comes to the offered treatments efficiency. We first need to know that for the sake of it, but also because public health is concerned; indeed, tinnitus is not only a big population concern, but also its treatments are often expensive, due to their duration. The evaluation of treatment efficiency is not easy because of several reasons due to tinnitus itself. These reasons are classical:

- (1) Absence of animal experimentation;
- (2) Absence of objective evaluation;
- (3) Interaction of somatic and psychic factors;
- (4) Interaction of natural evolution;
- (5) Difficulties to implement a convincing methodology for some therapies.

Especially, it is a problem to put together homogeneous subject groups.

Beyond the facts, the evaluation can imply the therapy team in different ways; for instance, by considering either that the tinnitus cause determines partly the evolution of the symptom or that the evaluation can consist of being part of the treatment, at a certain point.

The authors develop the evaluation methods and the different points.

As far as the therapy efficiency itself, its presentation is fast, if we consider what has been shown through the controlled and repeated studies found in the literature.

Introduction

Evaluating tinnitus is not an easy task. The difficulty of evaluating the therapy benefit is even bigger. From one person to another, according to individual personality and tolerance mechanisms, the impact is variable. It is indeed a multi-factorial symptom, and the benefits due to therapy are at different levels, too.

In helping patients, we automatically and in a non explicit way evaluate the degree of the tinnitus to adapt the therapy. The results of these individual evaluations are rarely correlated with those of the controlled trials.

Nowadays, the treatment efficiency is modest without being constant nor fast and the lack of treatments has caused multiple therapy propositions that have to be evaluated by valid methods.

Therapy evaluation is constantly addressed in every convention, with its same questions and warnings. We could merely repeat what has been said at the 1991 convention. However, we could make two

comments; on one hand, evaluating still seems more difficult considering the more important role of instrumental and counseling methods. Added to that, there is also the difficulty to evaluate the mixed therapies, with counseling, habituation development and use of drugs. On the other hand, the attempts to objectively give prominence to tinnitus are getting more numerous, giving hope for an efficient help.

We will have five main parts: the first presents the tinnitus evaluation methods, the second the treatment control. A short clinical study will illustrate the difficulties in the evaluation domain of therapy benefits. After a general discussion, we will finish by concluding on the role of the evaluation by the patient him/herself. There will not be any review nor therapy outcomes. Also, we will not deal with the mixed evaluations that involve an economic factor.

The subjective methods of tinnitus evaluation

In this session, we will systemically approach tinnitus evaluation and the benefits of pharmaco-

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logical therapies by defining the tinnitus aims, means, environment and temporal aspects.

Aims

In daily practice, the clinician makes a global evaluation of the tinnitus. The quality of this evaluation depends on his knowledge of the *tinnitus phenomenon* and also on the time spent on this evaluation.

In collective trials, prospective or retrospective, the aims are more numerous: it is first necessary to establish the efficiency of a treatment, but also to precise which patients can benefit from it, to interpret the therapy action mechanisms, and to record the secondary effects.

The main evaluation themes

Briefly, evaluating tinnitus in the context of therapy efficiency can be categorized into 4 areas:

- the description of tinnitus and the auditory status of the subject: a hearing loss combined with tinnitus defines heavily the handicap;
- the evaluation of the subject's personality;
- the evaluation of the tinnitus reduction;
- the evaluation of the handicap decrease.

Evaluating the therapy benefits is difficult because tinnitus is an intrinsically complex phenomenon, and for methodological questions as well: difficulty to characterize the subject psychological features, population hardly discriminated, varied evaluation date in the studies, absence of an agreed tinnitus classification, small number of controlled studies, absence of a simple animal model, absence of objective proofs, easy to implement in the clinical field . . .

All the evaluations require time (which may introduce a bias). Moreover, the evaluation has to be ideally complete because between the *psychoacoustical dimension* of tinnitus and the *handicap dimension* there is not always a relation. Thus, a unique evaluation in only one of these two domains does not allow to have a complete vision of the *tinnitus phenomenon*. Finally, to evaluate a treatment, it is necessary to precise its goals: reduction, masking, tolerance, and so forth.

Evaluation means of therapy benefit

At the moment, the different research teams have their own evaluation system. Most of them use an analog visual scale and a more or less long questionnaire.

(1) *Tinnitus classification*: The semi-structured interview will have to gather the general data concerning the patient and his tinnitus. The classification question would deserve to be developed. The classifications are numerous. We will use a classification on the less possible hypothetical dimension, in other words what the patient says. This approach is said to be "*a-theoretical*". This precise classification concern is not shared by all of us: categorizing

tinnitus seems to be secondary considering the importance of central mechanisms.

(2) *Evaluation of tinnitus intensity*: (a) *The scales*. Tinnitus intensity can be simply estimated with:

- an analog visual scale,
- a numerical scale,
- a verbal scale.

The scores have a descriptive value for a given subject and allow a follow-up. It is desirable to use the analog visual scale although it does not give any information on the exact nature of the complaint. Also, it cannot be used to compare the subjects among themselves. Nevertheless, it helps to identify the subjects needing to be taken care of, regardless of a direct relation between the obtained score and the kind of treatment. The numerical scales, usually from 0 to 10 or 0 to 100, allow to obtain a tinnitus measurement at the time of the consultation but also theoretically in a retrospective way. The numerical scales can be useful in case of comprehension difficulties that can be encountered in using the analog visual scale. The simple verbal scales are based on the choice of an adjective to define tinnitus intensity. The measurement is limited to 5 or 6 levels. These scales are often used for people having difficulty to use the previous 2 other scales.

The change sensitivity in the analog visual scale after treatment is considered as greater than with the 2 other scales.

Medicine consumption is not a good indicator to evaluate "tinnitus intensity".

(b) *Tinnitus descriptives*. It is a matter of showing the subject a list of qualifying terms characterizing his tinnitus. If each of these terms is to be considered as a separate information, the highest scores correspond to the existence of a more severe impact.

(c) *Improvement after treatment*. We could merely ask the question: "Have you noticed any improvement?". However, this procedure comes up against the problem of remembering the *ante* condition, before treatment.

(3) *Psychoacoustic methods*: We use matching or masking.

(i) *Loudness matching*. We use a loudness matching method between the "*intensity*" of tinnitus and the intensity of a pure tone. On a frequency point of view, the matching is done at the spotted tinnitus frequency or at a distant frequency, 500 or 1000 Hz, where we consider that audition is behaving more "normally" than in the tinnitus spotted frequency. Ideally, the psychoacoustic methods are based on the two alternative forced choice method. Since it is not easy to implement, we substitute to it a repetitive measurement repetition, and we note the measurement variability. From these values, we can calculate other values such as a sensation intensity measurement (dB SL). These methods aim to better reflect the psychoacoustic discomfort of tinnitus (see further).

(ii) *Minimal masking level (MML)*: We use a broad band masking noise to mask the tinnitus.

(iii) *Discussion on tinnitus intensity measurement.* The tinnitus evaluation procedures by matching usually give intensities of less than 10 dB SL for half of the subjects tested. An external noise audible at 10 dB HL is usually considered as weak for the majority of us. Evidently, recruitment plays an important role; by testing the tinnitus in relation to a signal at a frequency where we consider that the hearing behavior is normal, the masking levels are more important, more in relation to discomfort.

We can also consider that the intensity equivalent values show not only a general psycho-acoustic intensity function, but also a personal function. Hallam *et al.* [1] argue for transforming the sound levels in intensity personal unit based on the growth of the sone scale. This method tries to establish a personal growth sensation rule characteristic of each subject. It would better describe the sone growth. By transforming these values, Hallam [1] hoped to reduce the individual variance related to hearing threshold, recruitment, and sensitivity to loud sounds. In order to obtain the formula coefficients to use, we consider several values: the thresholds at different frequencies, the comfortable hearing level at 1 KHz (most comfortable loudness level = MCLL) and its multiples in intensity, and the white noise level necessary to mask the tinnitus. The measurements are done contra-laterally. These complex measurements are not systematically correlated to the distress or intensity experienced measured by other methods but they are correlated to some aspects of the psychological scales.

These psycho-acoustical methods show the importance of taking into account the relationship tinnitus/hearing status. As a general rule, the equivalence level expressed in sensation (dB SL) decreases progressively with the hearing loss increase at 1 KHz and at the tinnitus frequency as well.

(4) *Multidimensional scales – the questionnaires.* Evaluation tools have been created for a multidimensional tinnitus evaluation such as impact or explicative factors.

(i) *Questionnaire description and creation.* There are some open questionnaires, closed ones, and some lists of descriptives. The most used questionnaires are the closed ones because their exploitation is easier than in the others.

The difficulty in creating questionnaires consists more in their validation than in finding questions. A questionnaire has to meet metrological qualities: coherence, validity, test-retest reliability, change sensitivity. As a whole, a questionnaire must give an identical information even though it is obtained by asking questions formulated differently. It must also give information that can be supported by other means such as other validated questionnaires. It must give the same information even though it is submitted at close time intervals. Finally, it must be able to differentiate different subjects.

Coherence means that the questionnaire or the subgroup of questions deals with the same problem. To assess it, we look at the correlation between the responses at each question and a total score calculated based on the responses to other questions.

Without getting into details, this internal coherence measure is assessed by the Cronbach coefficient alpha, used to give an estimated figure of the questionnaire. A 0 value shows that every question is completely independent of the others. A coefficient 1 shows a perfect coherence of the questionnaire; indeed, the different questions are definitely related to the same underlying dimension.

The questionnaires drawn up for opinion surveys intended to the business world are not always validated. They look for and only take into account strong correlations. The questionnaires length is considered as less critical to the point where the “good responses” seem to occur only when the testee is “tired”.

The questionnaires exploitation consists in two phases: a descriptive phase and an explanatory phase. This one aims to show the explanatory factors of the studied phenomenon. Here again, we analyze in the global variability the importance of variability of each response.

The use of a questionnaire written in a foreign language raises the question of translation. Theoretically, to “retrieve” the questionnaire validity, its translation and retranslation in the original language have to give back the same worded questions.

(ii) *Cautions.* The validation of a long questionnaire version is not systematically stretchable to a short and truncated version of the same questionnaire. To study a specific point, if there is no validated tool in one’s language, each question has to be considered as a separate information. It is not right to add the scores in order to obtain a global score.

(iii) *The questionnaire main themes.* These multidimensional surveys deal with the tinnitus main themes: evaluation of the anxiety and/or depression factor, evaluation of the tinnitus impact on daily behavior . . .

(iiia) *The different types of questionnaires.* We have found in the literature 3 validated questionnaires. There exists some others, and lots of non-validated ones. The use of a non-validated questionnaire does not cancel its descriptive quality. It allows to define an average profile, and, for instance, to compare before/after treatment. This choice is based on the existence of a French translation.

(iiib) *The Tinnitus Handicap Questionnaire (THQ).* Drawn up by Kuk, Russell and Jordan [2], this questionnaire is conceived for the patient to measure the perceived degree of his tinnitus handicap. The THQ is a 27 item questionnaire. Its Cronbach rating alpha is 0.93. The questionnaire consists in 4 scales: life satisfaction, depression, physical health status, social insertion.

The factor analysis wants to show the correlation that can exist between the answers to the questions and a dimension or an underlying factor. The analysis in main components is a good statistical tool.

For this questionnaire, 3 factors have been identified:

- The factor 1 shows the tinnitus effects on social, emotional and physical behavior.
- The factor 2 reflects the patient hearing status.

- The factor 3 represents on one hand the subject's opinion of his tinnitus, if it is going to get worse, if he is going to get some help, and on the other hand the entourage's appreciation of his tinnitus.

The first factor explains 42.6% of the total variance, the second 9.4% and the third 5.6%.

Parallel to this question survey, the subject was going through hearing tests.

A small correlation was found between the THQ score and the tinnitus "intensity" level, the MML, and the health status.

A moderate (0.52–0.63) correlation was found between the total THQ score and the tinnitus intensity judgement, life satisfaction, the average hearing threshold, depression and the general health condition judgement.

The THQ reflects the hearing, emotional and physical status and the social behavior of tinnitus subjects.

The correlation between the subjective judgements of tinnitus intensity and handicap suggests that the tinnitus intensity could be a factor affecting the perceived handicap. However, the small correlation between the tinnitus intensity determined subjectively and pseudo-objectively (by the psycho-acoustical measurements) suggests that the subjective and objective measures do not apply to the same evaluation mechanism.

Finally, obviously the perceived handicap may not be due to tinnitus itself but results in part from the hearing deficiency.

(iii) *The Subjective Tinnitus Severity Scale (STSS)*. Created by Halford, Stewart and Anderson [3] in 1991, the STSS aims to estimate the tinnitus severity as far as intrusion, dominance and distress.

It consists in 16 items. The total score is calculated to reflect at once the tinnitus intensity, the emotional reaction and the handicap degree. A global severity rating is considered as impossible to be defined based only on the tinnitus impact on the patient's life. The STSS has a Cronbach rating of 0.84. The STSS is correlated differently with masking at 1 KHz and masking at the tinnitus frequency. This leads us to the discussion on measurement methodology as far as masking, but also on the following hypothesis: the subjective tinnitus experience would be more difficult to bear in a hardly perceived environment due to a hearing loss, and thus less capable of masking the tinnitus of the hearing impaired patient.

In practice, the STSS is a useful approximation to estimate the tinnitus severity.

(iiid) *The Tinnitus Reaction Questionnaire (TRQ)*. Created by Wilson [4] in 1991, the TRQ aims to evaluate the psychological distress due to the tinnitus. It consists in 26 questions. There is a 5 point scale. It is a forced choice procedure. The calculation procedure is a simple addition.

The Cronbach rating is 0.96. It seems that the TRQ is a reliable tool with a good internal coherence and a long term stability.

Four factors explain 66.4% of the variance. The factor 1, in a first series of questions, reflects the general distress and explains 50% of the variance. The factor 2 measures the tinnitus interference in work and leisure. The factor 3 is the one of severity. It covers the factor 2 but it deals with heavier distress signs. The factor 4 reflects the avoidance behaviors.

Measurement environment

A validation method of a measurement tool is to compare the results obtained with this method and the results obtained with other methods. The questionnaires do not avoid this validation. We can compare the questionnaires among themselves and compare them with the usual psycho-acoustic evaluation methods.

(1) *Relationships among the different questionnaires?* The personality structure is related to the behavior toward tinnitus. Moreover, we find a relationship quite obvious between the installation of tinnitus and the generating stress events, between the intolerance of a severe tinnitus and a stressing environment. Several studies have been conducted to establish the psychological profile of subjects suffering of tinnitus. In fact, the average profile does appear to be located within normal limits although individually we can find pathological personalities. The study of Meric *et al.* [5] has to be reported. Out of 281 subjects, the authors establish results comparisons between a French version of the Minnesota Multiphasic Personality Inventory (MMPI), a French translation of TRQ, THQ and STSS. Some correlations have been found between the MMPI scales and the THQ and TRQ scores. However, no relation was found between the MMPI and the STSS. This result could mean that despite the fixed goal, the score of this questionnaire is much more influenced by the tinnitus physical intensity than by the emotional response. This scale could be the best method to evaluate tinnitus when an evaluation as objective as possible is necessary. The numerous correlations that exist between the TRQ profiles and scores show that the emotional manifestations are correlated with the psychopathological profile.

(2) *Influence of hearing loss:* This subject has already been addressed. Let us precise again with that same study [5] that there is a significant difference between the normal hearing and the hearing impaired subjects in the distribution of the scores obtained in the three questionnaires. It seems that the daily life disruptions are more related to hearing loss AND tinnitus, rather than with tinnitus by itself. Thus, it is essential at once that the therapeutic strategies and the evaluations take this information into account.

Temporal aspects of evaluation

Tinnitus treatment is usually long. The subjects are periodically reevaluated but at present there is no

criterion to define the frequency of these reevaluations. It is left to the clinician's judgement and it is based on the goals fixed with the patient.

It is useful to consider that there are several critical dates as far as evaluation in non-medical domains as for instance in the case of opinion surveys after an interview or an announcement. Obviously, two dates are important: the 10th and the 40th day. For 10 days, the interview is sufficiently present in the subject's memory so that the tinnitus evaluation is influenced by a "guru effect". After 40 days, it is no longer the case and what is left in memory is more lasting. According to what we know, no clinical research deals with the problem of evaluation date in relation to therapy starting day.

All the tools proposed during the initial evaluation can be used for the follow-up. All the evaluations, the initial one and the following ones, are then compared. The required minimum is the tinnitus intensity measured by the tool initially used. The follow-up evaluation needs tools sensible to changes.

We consider that tinnitus tolerance is a function of modification of the tinnitus psycho-acoustical qualities but is also very dependent on psychological environment. These two components manage the general tolerance of tinnitus. There seems to be short term variations of tinnitus, for instance during the day, that depend on a neurosensorial mechanism (fatigue, noise exposure, . . .), and long term variations that depend more on psychological conditions and how it is felt. The reappearance of low tolerance is not necessarily due to sensation amplification. Finally, it is necessary to define treatment length and measurement number and dates (one or several measurements the same day?).

The measurements "before/after" depend on the reliability of the patient's memory. The tinnitus comparison of "before" can be as difficult as its reference date is far. Moreover, when the subject is asked to describe tinnitus intensity over a period of time, he unvoluntarily tends to describe the tinnitus actual degree or the degree where tolerance was at its worse point [6].

Psycho-acoustical measurement methods have the advantage to erase the appeal of the memorization process. Their disadvantage is that they are heavy. As far as tinnitus evaluation is concerned, all these biases must be present in the tester's mind who has to compromise. We could also measure treatment result quality in drug consumption. There exists no validated tool to keep track of medicine consumption or of the access of health system, or to know observance and self-medication. It is striking to note that sometimes, whether the subject believes his treatment to be efficient or not, he is definitely unable to remember the therapy speciality name. Likewise, whereas the treatment is said to be inefficient, it is often impossible to get him to stop it.

One tool is recommended as far as pain follow-up. It is the diary where the compliant patient can

note the medicine intakes, relief, and unbearable times. The aim is with no doubt reached as far as evaluation but we can wonder if the almost obsessive behavior of the measurement could introduce biases more detrimental than the lack of measurements?

Objective methods

Our wish would be to have an objective evaluation method of tinnitus for humans or, at worst, animals. We all wish to see the "tinnitus print", even though we are convinced that its repercussions are personal. We will not develop this chapter insofar as no reliable and usable clinical method allows to "verify" tinnitus, and thus to incorporate it into a therapeutic study.

Treatment control

Treatment control with a good measurement quality is a necessity for a collective evaluation of therapies. Indeed, when a treatment is prescribed, the subject expectations can influence the perception of relief.

As far as medical treatments, the situation is clear and well defined. In a therapeutical testing situation, using a placebo is the appropriate way. It consists in using the "real" treatment for a certain time period, and the placebo in another. In simple blind tests, the subject is not advised of the situation. In double blind tests, neither the prescriber nor the subject are advised of the kind of medication taken. The "cross over" method avoids the difficulty to match two groups of subjects.

(1) *The benefit of the therapeutical test:* The discomfort and distress improvement could be more in relation with the entrance into a therapy program than directly with its content.

(2) *Importance of previous treatment:* In a personal study, we find that 67% of the subjects had consulted an average of three doctors. Multiple treatments are offered: after a first therapeutic failure, the subjects often wish to follow another treatment. In fact, in a study of Andersson [7], the group of non-treated patients appeared less uncomfortable. We may think that these patients "free of all therapeutics" have more hope to find an efficient therapy.

The difficulty of evaluation in multiple treatments: If the efficiency of an only drug is difficult to prove, the utility of a polytherapy is much more delicate to establish. We also have to wonder about the presence of a potentially antagonistic effect. To develop rapidly habituation in the case of a peripheral vestibular destruction, it is recommended to avoid sedation treatments. Habituation in a matter of tinnitus seeks to create some new functional circuits that could suffer from the use of those sedative drugs.

Postal survey about the benefits of a medical treatment

In view of this presentation, we have worked on a small clinical study. It consists in an anonymous mailed self-questionnaire. The sample consisted in subjects having consulted the same doctor. One hundred thirty (63%) persons have responded out of 204, resulting in 119 exploitable responses.

The questionnaire consists in 2 parts:

- the first part consists in the French translation of the Wilson's TRQ questionnaire;
- the second part is a 2 branch questionnaire aimed to compel a clear and unambiguous response:

“the treatment has modified the tinnitus”

“the treatment has in no way modified the tinnitus”

It is not a validated questionnaire.

The objective of the first questionnaire (TRQ) is to place our population in relation to Wilson's population.

The objective of the second questionnaire is:

- to track down the behaviors that apparently are illogical: the treatment has in no way modified the tinnitus but I still follow it.
- to know if the tinnitus modifications resulting from the treatment are more related to the psychoacoustical modification of tinnitus and/or related to day and night tolerance of tinnitus.
- to evaluate the follow up of an anti-epileptic benzodiazepan: Clonazepamfi.

Two treatments are notoriously efficient: lidocaine and direct current. However, they are not usable in a permanent way. The other treatments are divided between 2 groups: the logical treatments based on an acknowledged mechanism such as epilepsy or pain, and the recipe treatments, without any validated justification. To recapitulate the conclusions of Simpson's article [9], usually all the medical prospective trials end up with the same result. The positive repliers are more numerous than the negative ones but the global study does not show any improvement. The reasons are more or less obvious such as statistical reasons or reasons related to sample heterogeneity. In this study, the choice of Clonazepam is related to the global efficiency feeling on tinnitus.

Before giving a few results, it is obvious that the statement “the treatment has or has not modified the tinnitus” is an abusive conclusion.

This study essentially shows the difficulty to evaluate with no reference point before treatment.

(1) *The TRQ questionnaire results:* The average of the total additions is 37.2 with a standard deviation of 14.8 for $n = 128$. In Wilson's study, in the sample of subjects concerned by tinnitus, the average for 50 subjects was 36.12 with a standard deviation of 26.01.

We can with no doubt consider that tinnitus is not different from one study to another. Indeed, the

items scored 4 or 0 50% or more of the time, and the list of items scored 3 or 4 20% or more of the time is more or less identical.

(2) *The descriptive questionnaire results:* 32% (38/119) have responded that the tinnitus is modified.

The modifications: In the psycho-acoustical domain, the modifications are not straightforward. For only one subject has the tinnitus disappeared. The modifications do not concern neither pitch (64% respond it has not changed – 24/38), nor stability (82% respond it is not more stable than it was – 31/38). Regarding the tinnitus discomfort, 16% (6/38) only respond that the tinnitus does not bother them anymore but that there are better times (42% – 16/38). They no longer spend their time checking the tinnitus is still present (63% – 24/38). However, they still look for a masking (55% – 21/38).

The tinnitus is no longer bothering at work (82% – 31/38).

As far as sleep, the results are mitigated: 47% fall asleep easily (18/38).

68% of the subjects respond that the treatment has in no way modified the tinnitus.

Among them, 59% (52/88) have stopped the treatment and 41% pursue it even though no change has happened. Pursuing the treatment is related for 11% of the cases to hope for a future improvement, and for 8% because they feel better with it.

As a whole, these results show that 43% (52/119) have stopped the treatment. In about 1/3 of the cases, there have been some modifications. These essentially concern the fact that there are better time periods and that there no longer is an obsession for tinnitus measurement.

As far as Clonazepam is concerned, 57 persons (44%) have used this therapy. Forty six percent have stopped the treatment, 46% have pursued it, and 8% have not responded.

General discussion

Our evaluations aims, on one hand, to give an objective tinnitus level, or rather a noise representation. On the other hand, we measure the subjective aspect of tolerance, either with a certain distance (multi-dimensional survey), or as a whole by using a “I can no longer stand” scale. There are 2 measurement levels: the phenomenon representation and the tolerance measurement.

After the therapy, we often get to the following acceptable situation: “it still hurts the same (objective evaluation) but I no longer suffer (tolerance evaluation)”, or rather “my tinnitus is still here but it no longer bothers me.”

Regarding the level of scientific proof, the ANAES (Agence Française de l'Evaluation Médicale) gives the following classification:

Level of scientific proof:

- I. big controlled comparative trials with unquestionable results,
- II. small non-randomized comparative trials and questionable results,

III. non-randomized comparative trials with a group of contemporary control subjects,

IV. non-randomized comparative trials with a group of historic control subjects,

V. no group of control subjects, series of patients.

The recommendations deducted from these studies have a certain “strength”, a grade:

A. level of proof I,

B. level of proof II,

C. level of proof III, IV, V.

In the absence of level of proof, the recommendations given correspond to a professional agreement.

As far as the lost patients, they could be resigned, satisfied, or have consulted somewhere else.

Conclusion: the moment of evaluation

The treatment measurement can be a doctor’s self-satisfaction. But it is also a time when the doctor distinguishes the true from the false. The evaluation is a therapeutic time. We go from fantasy to objectivation by the group. The satisfaction questionnaires represent an evaluation of the recovery, not by the doctor but by the patient. The subject gives an opinion on something other than the medical anatomo-clinical efficiency.

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Tinnitus as an unwanted outcome of medical and surgical treatments

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While tinnitus is widely prevalent in otologic practice, it is not sufficiently appreciated how medical or surgical procedures might induce or modify pre-existing tinnitus or make the management of the tinnitus more difficult. Although tinnitus may frequently be reduced by some otologic procedures (i.e. successful stapes surgery), it can also occur after routine procedures without overt technical difficulties or complications. In addition there appears to be a small sub-population of patients in whom the emergence or exacerbation of tinnitus is in close temporal relationship with administration of drugs, most commonly psychotropic medications. Both of these categories of patients are difficult to manage because they blame themselves for allowing the medical intervention or surgery to be performed, thus providing themselves continuous negative self-counseling.

The emergence of tinnitus as a side effect of surgical procedures is inevitable in a small percent of cases, and proper pre and post-surgical counseling can decrease the impact of tinnitus in such cases. There is need for specific counseling of all patients undergoing surgery involving the ear or auditory pathway to decrease the probability of the emergence of clinically significant tinnitus. In addition, we must keep an open mind whether certain medical treatments might contribute to the origination or exacerbation tinnitus.

Introduction

Tinnitus is a common and often difficult otologic symptom to manage in the best of circumstances. It can be all the more difficult when the patient perceives that the tinnitus is the result of a medical or surgical intervention. This report will review the patients seen at the University of Maryland and Emory University Tinnitus and Hyperacusis Centers who attributed the onset of their tinnitus to a medical intervention. This report is subject to a number of caveats from the outset.

First, the evidence for the association of the tinnitus is a temporal correlation; thus it is difficult to determine if there is a true causal relationship or an unrelated co-incidence. Tinnitus is a common symptom and the probability of a few patients developing tinnitus while on any drug or therapeutic regimen is high. None-the-less, we have noted a few patterns that we believe are real and cannot be entirely dismissed as coincidence.

Second, we have no access or means to determine the total number of patients at risk for these occur-

rences, thus we cannot compute any incidence or relative risk data for the treatments or medications described.

Methods and results

A total of 722 patient records from University of Maryland and Emory Clinic Tinnitus and Hyperacusis Centers were reviewed. 164 records were excluded because they did not detail the specifics of the onset of tinnitus, leaving a total of 558 charts for detailed review. The self-reported etiologies of the tinnitus included uncertain etiology – 294 (53%), acoustic trauma – 88 (16%), upper respiratory infection – 38 (7%), and other miscellaneous causes – 9%. Eighty-six patients, or 15.3% of the total attributed the onset of their tinnitus to some medical intervention. These patients were divided among the following categories for further analysis: sound injury – 24 patients, surgery – 19, pharmaceuticals – 36 and miscellaneous interventions – 7.

Sound injury accounted for 24 patients representing 4.3% of the total group and 28% of the medically related tinnitus (Table 1). The largest group in this category, 12 patients, attributed the onset of their tinnitus to dental drilling. The second two largest groups directly relate to otologic practice. Five patients developed tinnitus after they were subjected to suction or irrigation of cerumen from the

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Table 1 Sound injury causing tinnitus

| | |
|-------------------------------|----|
| Audiogram | 3 |
| Cerumen irrigation or suction | 5 |
| Dental drilling | 12 |
| Hearing aid | 2 |
| MRI scan | 1 |
| Tympanometry | 1 |

external auditory canal. Six additional patients attributed tinnitus to some audiologic procedure including standard audiograms, hearing aid use or fitting and tympanometry.

Nineteen patients attributed their tinnitus to surgery; 14 to otologic surgery and five to non-otologic surgery (Table 2). The most important group in this category was stapedectomy, which accounted for 7 of the 19 patients in this group. The remainder of the cases were mostly middle ear procedures, there were two procedures involving the mastoid.

Table 2

| | |
|--|---|
| <i>Tinnitus related to surgery: Otologic surgery</i> | |
| Exploration of middle ear | 1 |
| Fistula repair | 1 |
| Labyrinthectomy | 1 |
| Mastoidectomy | 2 |
| Myringotomy | 1 |
| Stapedectomy | 7 |
| Tympanoplasty | 1 |
| Other ear surgery | 1 |
| <i>Tinnitus related to surgery: Non-otologic surgery</i> | |
| Angioplasty | 1 |
| Coronary bypass | 2 |
| Facelift | 1 |
| Spinal fusion | 1 |

Pharmaceuticals were considered the cause of tinnitus in 36 of the patients, accounting for 6.5% of the total series and 42% of the medically related patients. The categories of drugs taken by patients before onset of the tinnitus included psychotropics – 14, analgesics/NSAIDS – 5, antibiotics – 7, cardiovascular drugs – 4, and miscellaneous – 6. Tricyclic antidepressants were the largest single group among these, accounting for 7 patients (Table 3). Among the non-psychotropic drugs there were 18 different drugs or drug combinations, four of which were reported by two patients and 14 represented by only single reports.

Table 3 Pharmaceutical related tinnitus.

| | |
|-------------------------------|---|
| Psychotropics | |
| Serotonin reuptake inhibitors | 5 |
| Tricyclic antidepressants | 7 |
| Other psychotropics | 2 |

Discussion

Sound exposure

Patients frequently report the onset of tinnitus in association with a single episode of moderate to

loud sound exposure. Tinnitus with or without associated hearing loss has been reported after high intensity noise exposures such as explosive injuries, compression tool noise, wireless telephones, and automobile airbag deployment. However, more trivial sound exposures not associated with hearing loss can also cause tinnitus. Although we were initially skeptical about the validity of these reports, the cumulative anecdotal experience, especially those not under litigation, suggests this is a real phenomenon.

In otologic practice the most likely source of significant sound exposure is the vacuum aspirator or irrigator used for cleaning cerumen of the external auditory canal. A large bore suction (e.g. # 7 Baron tip) can generate a significant amount of sound when it is initially obstructed with cerumen and this debris suddenly breaks free and travels up the suction. Caution should manipulation of the ear and the use of instrumentation around the ear should minimize the incidence of these complications.

Otologic surgery

Tinnitus may often be helped by otologic surgery for hearing restoration, but it is also a known complication. Tinnitus is common in patients with otosclerosis; Glasgold and Altmann (1966) reported 79% of unoperated patients had tinnitus. In those with successful stapes surgery (air-bone gap <15 dB) tinnitus was eliminated in 31%, improved in 33%, unchanged in 23% and worse in 3%. [1] Similarly Sakai *et al.* (1995) found the tinnitus score was improved in 68%, unchanged in 27% and worse in 5% [2]. Age does not seem to have a detrimental effect on these results. Proschel *et al.* (1993) examined 105 patients who underwent partial stapedectomies at the age of 65 years or older as treatment for combined hearing losses due to otosclerosis. They found that tinnitus decreased or vanished in 75% of the cases [3]. Despite these encouraging results, the development of tinnitus after successful or, more commonly, unsuccessful stapes surgery, appears to be unavoidable in a small percent of cases.

Although none of our patients complained of tinnitus in relation to surgery for an acoustic neuroma, this subject merits discussion here. Tinnitus is a common preoperative complaint in patients with acoustic neuroma, occurring in 60% to 80% of patients [4]. Reports in the literature give a very mixed picture of the incidence of tinnitus after surgery for acoustic neuroma regardless whether hearing is preserved or not preserved. Silverstein reported that among hearing preservation procedures, 38% of patients with tinnitus were improved, 37% unchanged, and 25% worse after surgery [5]. Kanzaki *et al.* (1999) reported a higher incidence of tinnitus after hearing preservation surgery than when labyrinthectomy was a part of the procedure. In their series, 85% of patients without tinnitus developed it after hearing preservation procedure whereas only 31% of non-hearing preservation patients developed new tinnitus [6]. Matthies

and Samii (1997) found the incidence of preoperative tinnitus was higher in hearing than in deaf patients; however, preoperative deafness did not mean that the tinnitus would be relieved by surgery; tinnitus persisted in 46% of preoperatively deaf patients [7]. Berliner *et al.* (1992) reported that patients who reported preoperative tinnitus tended to show small but statistically significant improvement in the perceived severity of the tinnitus after surgery, although the symptom rarely resolved entirely. Conversely, those with no preoperative tinnitus have an approximately 50 percent chance of developing it following surgery [8].

Cochlear nerve section has been promoted for the management of tinnitus in deaf or profoundly hearing-impaired patients. Success rates between 45% and 95% have been reported. The strongest proponent of this procedure is Pulec (1995) who states that of 151 patients, complete relief of tinnitus was achieved in 101, worthwhile improvement was obtained in 43 and 7 patients obtained no improvement [9]. Other authors have been much less optimistic about this procedure. For instance, McElveen *et al.* reported only 11% of patients were tinnitus free and another 24% better after cochlear nerve section [10]. In a small series House and Brackmann (1981) noted 60% of patients' tinnitus was worse following this procedure [11]. These data suggest that cochlear nerve section is a less than satisfactory alternative for patients in whom tinnitus has developed as a result of otologic or neurotologic surgery.

Medication

Patients frequently report the onset of tinnitus coincident with the initiation of a new drug or with the upward adjustment of the dose of a drug. The Physician's Desk Reference Companion Medical Guide® lists over 260 drugs as having tinnitus as a potential side effect [12]. However, most of these data are collected from open-ended queries in which patients were asked to list any presumed side effect. From these reports, it is not clear if the emergence of tinnitus is causally related to the drug or coincidental. Among patients seen in the University of Maryland and Emory Tinnitus and Hyperacusis Centers, there does appear to be a small sub-population of patients in whom the emergence or exacerbation of tinnitus was in close temporal relationship with administration of drugs, most commonly psychotropic medications. These reactions represent a tiny fraction of patients given these drugs and the occurrence remains completely unpredictable.

The development of tinnitus after medical intervention remains unavoidable in a small percent of cases. Whether the tinnitus is truly causally related to the medical therapy or not, the relationship remains fixed in the mind of the patient. The important issue is how the treating physician responds to the patient's concerns. As pointed out by Hazell (1990), the perception of the tinnitus and thus the impact on the patient's life may be

enhanced by feelings of regret for having had the procedure or taken the medication [13]. In addition, there may be hostility toward the surgeon or physician who suggested or performed the intervention. Thus, the patients provide themselves continuous negative counseling regarding the tinnitus and the operative procedure, which may be enhanced by apparent insensitivity on the part of the care provider.

Management of the patient at this juncture is important to avoid compounding these feelings with negative feedback or counseling by the treating physician. The management most appropriately starts preoperatively with a discussion of complications and their management, including the emergence of tinnitus. Elements of directive counseling such as used in Tinnitus Retraining Therapy might be included in the preoperative counseling to stress that even if tinnitus emerges it can be helped in the majority of cases. It should be emphasized that the emergence of tinnitus does not necessarily equate to a surgical mishap or complication. The perception of tinnitus itself does not result in discomfort the vast majority (>75%) of cases and occurs in everyone given an appropriately quiet environment. Physicians must be as understanding and supportive of these patients as they would be with any patient with a complication or sub-optimal result.

We have raised the issue of cochlear nerve section in the treatment of tinnitus because it appears on the surface to be an easy alternative in the management of the patient with a poor hearing result and disturbing tinnitus. The evidence from acoustic neuroma surgery suggests that resection of the acoustic nerve does not prevent or ameliorate tinnitus in a high enough percent of cases to make it a realistic alternative for most patients. Furthermore, nerve section permanently prevents the use of sound therapy, electrical stimulation or cochlear implantation in the management of these patients.

In summary, the nature of the relationship between medical interventions and onset of tinnitus remains a difficult one. Although a mechanism may not be apparent, our experience is that tinnitus can develop coincident with some medical interventions. We have successfully applied Tinnitus Retraining Therapy (TRT) to many of these patients.

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How TRT derives from the neurophysiological model

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Habituation of tinnitus-evoked reactions and the perception of tinnitus-related neuronal activity have been proposed on the basis of the neurophysiological model of tinnitus. Habituation is a normal, common, and necessary function of the brain. Its necessity results from constraints in the brain's ability in performing multitasking behavior (the brain cannot handle more than one conscious task at any given time). To cope with the large amount of sensory information that reaches us all the time, our CNS selects and blocks all unimportant stimuli from reaching our awareness at subconscious level. It also blocks reactions which these stimuli would otherwise evoke, i.e. habituate. Notably, the selection and blockage of unimportant signals must occur at a subconscious level on the basis of the past experience. The selection process cannot be done on a conscious level, as it would consume our attentional abilities and nullify the purpose of selection.

The primary clinical goal is to habituate reactions of the limbic and autonomic nervous systems. The secondary goal is to achieve habituation of the perception. Note, that even when a very high level of habituation of the reaction and perception is achieved it is still not a cure for tinnitus, as patients can hear their tinnitus anytime when they focus their attention on it; and the tinnitus pitch, loudness are the same as at the beginning of the treatment.

While some patients achieve a high level of tinnitus habituation, to be of clinical significance habituation does not need to be complete, and patients can experience significant improvement even with partial habituation of reactions and perception. The final goal of the treatment is that tinnitus ceases to have an impact on the patient's life. Since the habituation-related modifications of the nervous system occur above the source of tinnitus, the etiology of tinnitus is irrelevant, and therefore any type of tinnitus, as well as somatosounds, can be treated by inducing their habituation.

Habituation can be achieved or facilitated by a number of approaches, including counseling combined, for example, with medications, biofeedback, hypnosis, etc. The easiest implementation of Tinnitus Habituation Therapy (THT) involves the parallel use of retraining counseling with sound therapy. This therapy has become popular under the name of Tinnitus Retraining Therapy (TRT). These two components perform different functions and both have to be used for a method to be called TRT.

Retraining counseling acts to decrease the level of stimulation from the cortical areas of the brain to the limbic and autonomic nervous systems, and to decrease the general level of activity within these two systems. The crucial point to recognize for both the therapist and the patient is that since tinnitus-induced reactions are governed by the conditioned reflex principle, the conscious realization of the benign nature of tinnitus is not sufficient to remove these reactions, and therefore a significant amount of time is needed for their gradual extinction.

Sound therapy provides significant help in the process of habituation by decreasing the strength of tinnitus-related neuronal activity within the auditory system, and from the auditory system to the limbic and autonomic nervous systems. Consequently, the strength of tinnitus-related activation within all loops decreases, making habituation of tinnitus easier.

All our senses are acting on the principle of gradient, or difference between a signal and its background. The absolute physical intensity of a stimulus is secondary. The same sound appears louder and evokes more detectable change in the neuronal activity when there are no other competing sounds. When the same sound is presented with some additional auditory background it appears to be softer, and the neuronal activity evoked by it become more difficult to detect. Presently, we cannot directly decrease the tinnitus-related neuronal activity, however, by enhancing background neuronal activity, by exposing patients to low level sounds, the relative strength of the tinnitus signal decreases, facilitation habituation.

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tions and, as a consequence, act particularly on positive emotions. (5) Every reflex undergoes extinction when reinforcement is removed, and sensory stimulus is repeated. (6) Habituation of reactions induced by stimuli and their perception is an integral and necessary function of the nervous system. (7) The nervous system works in the dynamic balanced scenario. (8) The strength of any signal in the nervous system is related to its difference with background neuronal activity. This difference should be understood as involving a multi-dimensional space of parameters, including the properties of temporal patterns of the signal vs. random spontaneous activity, and activation induced by other stimuli. (9) All of the interactions within the nervous system are highly nonlinear and exhibit stochastic resonance (e.g., addition of a low level of noise can decrease the threshold of detection of the stimulus and enhance it, when the stimulus is weak and close to the threshold of detection). (10) The brain is active during sleep (e.g., restoration of biochemical balance, consolidation of memory, high level of ongoing activity, with a close resemblance, during the Rapid Eye Movement stage of sleep, to the activity observed in the state of awakeners), with the lower levels of the auditory system having very high levels of activity.

Keeping in mind the principles of neuroscience described above, we are now able to discuss how they are related to the neurophysiological model of tinnitus, and what practical implications we can draw from the model in providing help to tinnitus patients.

The auditory, limbic, and autonomic nervous systems, together with the cortical area involved in memory, and attention, are among the systems interacting to produce a phenomenon of clinically-relevant tinnitus signal. According to the model, it is not the perception of tinnitus, but the presence of inappropriate associations between tinnitus-related neuronal activity and the reactions of the limbic and autonomic nervous systems, which are responsible for tinnitus-induced distress, creating a clinically-significant tinnitus.

The fact that information processed in the nervous system modifies the neuronal networks and induces plastic changes, offers an opportunity to purposely reorganize the neuronal networks and their connections, which were induced when the conditioned reflexes responsible for tinnitus distress were created.

The reactions induced by tinnitus are linked with the tinnitus signal following the principle of conditioned reflexes. Including this point in the model allows for explanation of many features of tinnitus and offers a potential solution to the problem. It is well recognized that any kind of conditioned reflex can be reversed and retrained by the proper techniques. If the problem arises from creating inappropriate conditioned reflex arcs, those connections can be retrained and the habituation of reaction and perception of tinnitus can be achieved. This process would follow the principle described below by Konorski in 1967 [5], following the original postulate from Pavlov in 1928.

“When a stimulus is repeatedly presented without being followed by any arousal-producing consequences, these effects are gradually attenuated and some of them may be eventually totally abolished. This phenomenon, originally denoted by Pavlov as ‘extinction of orientation reaction,’ is now usually called ‘habituation’” [5].

Habituation is a natural, inherent feature of the central nervous system and, once initiated and sustained, can provide relief for tinnitus patients. The approach that was aimed at habituation of tinnitus-induced reaction and tinnitus perception can be labeled Habituation-Oriented Therapy (HOT) or Tinnitus Habituation Therapy (THT). The final goal would be to achieve total habituation of the reaction and perception of tinnitus (some patients are accomplishing states very close to this ideal). From a practical perspective, it is sufficient for a patient to achieve only partial habituation of reaction to experience significant improvement.

Significant habituation of reactions induced by tinnitus is our primary clinical goal. It is important to recognize that the habituation of perception is secondary. It will accompany habituation of reactions to various degrees but, for a successful treatment outcome, it is of great importance that patients recognize these priorities. Otherwise, they will be endlessly searching for the “holy grail” of not hearing tinnitus anymore or thinking that they will acquire complete silence.

There is no doubt that some positive improvement can be achieved in tinnitus patients by the use of specific medications (e.g., psychotropic drugs decreased the activity of the limbic and autonomic nervous systems) or by the improvement of a patient’s well being (e.g., counseling aimed at coping and relaxation), but in the majority of cases, this will only be of temporary help. All of the systems involved in the processing of the tinnitus-related neuronal activities are connected in a dynamically balanced scenario. General decreases in activity within the limbic and autonomic nervous systems will not produce changes in specific tinnitus-related connections, if not accompanied by other techniques offered by TRT (e.g., general decrease of the tinnitus signal by sound therapy, understanding of mechanisms of both tinnitus and brain function to “know your opponent”).

A partial decrease in the strength of the tinnitus signal acts synergistically with the decreased activation of the autonomic nervous system and should facilitate the habituation process. The issue which remains open is how to sustain the habituation with a constant need to keep the patient on medications or therapy, as these really are not aimed at the problem itself (tinnitus) but rather the distress developed as a consequence of the problem!

High levels of activation of the autonomic nervous system, thought the principle of contrasting drives, radically decreased patient’s quality of life, enhance tinnitus-induced distress, and frequently results in depression. Reactions induced by tinnitus

(e.g., activation of the autonomic nervous system) serve as a negative reinforcement in the conditioned reflex arc, which, together with the constant presence of tinnitus, become self-sustained.

Extinction of the tinnitus-induced reflex is achieved by partial attenuation of reactions, reclassification of tinnitus perception, and a decrease of intensity in the tinnitus signal by reducing its difference with ongoing neuronal activity. Once tinnitus is reclassified into the category of neutral stimuli it will be gradually habituated, similar to other unimportant stimuli.

Habituation can be achieved by a variety of methods, but counseling, which provides information, teaches and helps in setting up proper goals and expectations, is a crucial component of habituation-oriented approaches. Proper counseling, based upon the neurophysiological model, helps to decrease the strength of connections from the high level cortical areas to the limbic and autonomic nervous systems, and initiates the process of reclassification of the tinnitus signal stored in memory.

As the systems involved in processing the tinnitus-related neuronal activity are connected in a dynamic balanced scenario, in theory, it should be possible in some patients to achieve habituation of tinnitus by counseling alone. However, this is not a practical approach. A partial decrease in the strength of the tinnitus signal had a synergistic action with a general decrease in the activation of the autonomic nervous system, caused by proper counseling, and should facilitate the process of habituation. This general decrease can be achieved by a number of methods, including relaxation techniques, hypnosis, biofeedback, etc.

In practice, the use of sound is optimal due to two main factors. The first one is related to the role of the background neuronal activity in changing the strength of the tinnitus signal, with the additional possibility of reversing hyperacusis. Evaluation of the signal comparing it to the background neuronal activity is the basis of our perception. Following this principle, by increasing background neuronal activity, it is possible to effectively decrease the strength of tinnitus-related neuronal activity within the auditory pathways and consequently in all systems involved. As this signal is transmitted to the cortical areas and the limbic and autonomic nervous systems, its decrease will result in a decrease in the strength of activation in all of the systems involved, as per the dynamic balanced scenario.

The background neuronal activity consists of a spontaneous and evoked components, and change is achieved by increasing the evoked component. By exposing subjects to a variety of low level sounds, a decrease in the difference of tinnitus and the background neuronal activity is achieved. Precautions should be taken not to use too low levels which could be close to the threshold levels of sound perception, as these could enhance the tinnitus signal due to the stochastic resonance.

Stochastic resonance is well established and a

proven phenomenon in neuroscience and described as an enhancement of detection of weak signals paradoxically resulting from mixing the signal with low level noise. Whereas, the effects of stochastic resonance have been shown in a number of systems in the past, recently it was documented to exist at the level of hair cells and the auditory nerve [6,7].

The second factor which justifies the use of sound is related to hyperacusis. At least 25% of tinnitus patients require specific intervention to remove hyperacusis. Obviously, in such a case the use of sound is fundamental, because it is used to desensitize the auditory system and effectively remove hyperacusis.

It was shown that the auditory system was very active during sleep, particularly at the lower levels of the auditory pathways. This is why the use of sound during the night is beneficial. Additionally, when considering patterns of sleep which include the periods of shallow sleep awakenings, sound present in the environment during the night decreases the contrast between the tinnitus signal and the background.

Another practical issue, which has not been sufficiently discussed, is about the rules of what minimal requirements are needed to consider a method to be TRT. They can be summarized as follows:

- (1) The concept of the neurophysiological model should be accepted and used as the basis for diagnosis and treatment of each patient. A specific treatment protocol, individually adjusted to each patient, should follow the guidelines outlined in the patient categories corresponding to the model.
- (2) A tailored for each patient, one-on-one counseling session, is first of the two main components of the treatment for tinnitus. Discussion regarding the patient's condition, a simple explanation of the model, and questions and answers focusing on the neurophysiological basis of the treatment should be included in the counseling session. A series of systematic follow-up appointments, involving additional one-on-one counseling, should be scheduled over a period of 2 years.
- (3) The proper use of sound therapy following the rules of the model, but not necessarily the use of noise generators or hearing aids, is an integral part of the treatment.

Neither the neurophysiological model of tinnitus nor TRT should be considered as final, fixed entities that do not change. In fact, the opposite is true. New discoveries in neuroscience are continuously incorporated into the model and their implications transferred into the modifications of TRT. A good example is an explanation for the proper use of sound levels offered by the latest work on stochastic resonance.

Another challenge relates to the efficacy of TRT and discussions of the nature of medical evidence.

When considering Professor Maran's statement [8] regarding the validity of medical procedures, TRT at this time would not fulfill his requirements. Hypothetically, to evaluate TRT, one can design a randomized trial with some agreeable controls. But the validity of this study, time frame and the sample of patients will be questionable and face many ethical issues. Keeping in mind the lack of objective tinnitus measures, it would seem that the most appropriate method for the evaluation of the efficacy of TRT would be by the method called "evidence by consensus".

The experimental methods are valid only to the extent that they are replicable and therefore accepted by the scientific community, i.e. informed consensus is the ultimate proof. When replication of the experimental results (including clinical studies) is not achieved, the consensus is missing and the results are invalidated. For this purpose, easy, short and self-explanatory questionnaires were designed [9] and a database created to facilitate multi-center studies to validate TRT by clinical experience. The meta-analysis will then be applied. This method will allow to "aggregate results from many studies, combine subjects and evidence from all studies, thereby generate a more stable estimate and greater power than that derived from any of the single studies. This ability to generate more generalizable results through meta-analysis is true even if there are a number of larger-scale trials in the literature, because the combined evidence speaks more powerful than the individual parts either to unequivocally confirm and quantify the magnitude of an outcome across studies that can then guide policy or to help identify and provide explanations for conflicting results" [10].

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The TRT method in practice

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Tinnitus retraining therapy is one approach by which habituation to tinnitus and hyperacusis can be induced. It is logically based on the neurophysiological model described by Jastreboff (1990) [1]. Considering the complexity of tinnitus and hyperacusis, it is logical and straightforward, both in treating the patient, and in teaching the technique to health care professionals.

The key problem with persistent tinnitus and hyperacusis is an aversive conditioned reflex response, similar to that evoked by security issues, or threats to wellbeing. For as long as this response to internal neuronal activity (in tinnitus) or external sounds (in hyperacusis) is established in the subconscious, it continues to evoke unpleasant alteration of limbic and autonomic function, whenever the signal is detected. Habituation to continuous meaningless sounds occurs rapidly, but does not occur where the sound has a negative, invasive, or threatening message. The goal of TRT is to habituate or block completely any reaction of the limbic or autonomic nervous system to tinnitus, or, in hyperacusis, to sound in the environment, which is causing annoyance. The technique requires a specific approach in which tinnitus and hyperacusis is first categorised, and an individual programme of retraining on a one-to-one basis is designed for each patient, dependent on 5 different treatment categories. All treatments involve directive counselling/teaching, training in sound enrichment of the environment and avoidance of silence. Some categories involve the use of instruments (either noise generators or hearing aids), fitted and used in the specific context of the neurophysiological model. The vital component for both professionals and patients is a complete understanding of the model.

TRT assessment and diagnosis

Before beginning TRT a full ENT and audiological assessment will be made using the best practice criteria. Treatable otological conditions will be managed in the usual way, with particular care being taken not to make tinnitus worse. Increasing patients fears about the malignant nature of their tinnitus must be avoided, particularly when it is necessary to exclude an acoustic neuroma, or in performing surgery which often results in a quite predictable temporary increase of tinnitus postoperatively. In this instance problems can be avoided by proper preoperative counselling, with an understanding of the neurophysiological model, which explains why tinnitus is louder when the ear is blocked with dressings/blood clot.

By diagnosis in TRT we mean the division of patients into specific treatment categories, according to their experience of tinnitus and hyperacusis. This greatly increases the chance of successful treatment. Thus category (1) patients have significant tinnitus, (2) significant hearing loss with tin-

nitus, (3) hyperacusis, (4) hyperacusis with prolonged symptom enhancement by environmental sound exposure, and category (0) have minimal symptoms, not requiring prolonged intervention. Each of these categories requires a different approach, and wrong treatment can make patients much worse, particularly in category (4). It is also important to exclude the possibility of Lyme disease in this category. In each case the diagnosis is dependent on the evaluation of the problem, rather than on audiometric data, so a high frequency hearing loss on the pure tone audiogram without significant hearing difficulty would not put the patient into category (2). In categorisation we are looking for the dominant factor.

Forty percent of tinnitus patients have a degree of hyperacusis [2]. The mechanism is very similar to the emergence and persistence of tinnitus, although in hyperacusis the source of the aversive stimulus is in the patient's external environment, rather than being part of the auditory system. Patients with sound sensitivity need to be assessed by the degree of pure hyperacusis (sensitivity to all sounds), and phonophobia (sensitivity and aversion to specific sounds, without any sensitivity to others). In practice hyperacusis and phonophobia co-exist in varying proportions. An understanding of the

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reasons underlying the reason for phonophobia is essential for appropriate directive counselling which is an important part of the treatment.

The purpose of TRT is to induce habituation, first of the reaction (of the limbic and autonomic nervous system) to the tinnitus signal, and subsequently to habituate the perception of tinnitus itself (although this is not the primary goal). A method of measurement of these parameters is needed to assess the strength of the reaction, (annoyance or distress caused by tinnitus) and the extent of perception (awareness of tinnitus). These parameters can be conveniently recorded as the percentage of waking hours when the tinnitus is experienced (percentage awareness) and the percentage of waking hours when the tinnitus is distressing or annoying (percentage annoyance). New patients may require encouragement to differentiate their tinnitus in this way, as severe tinnitus can be 100% annoying and distressing. If preferred, an analogue scoring chart may be used. In addition we note any activities or 'life factors' which are prevented or interfered with by tinnitus, such as sleeping, concentration, quiet recreational activities, sport etc. A simple record is made of the number of activities interfered with. This approach allows the following questions to be answered:

- what is the severity of the problem (percentage distress)?
- has some habituation of reaction already occurred?
- is distress largely absent? (Category (0) patients)
- after treatment, has the patient achieved a successful result?

In calculating success of treatment we use the percentage improvement in awareness and annoyance together with the number of life factors that have been facilitated. Using the '40% rule' (our practice) patients are assessed as being successfully treated, or graduated, if they have a 40% improvement in annoyance and awareness, or a 40% improvement in annoyance or awareness, plus a facilitation of one life factor.

Audiometric evaluation is always required but the emphasis is different than in conventional audiology. Pure tone audiometry at all fixed frequencies is combined with loudness discomfort levels (LDL) at each frequency. This gives a measure of hearing, and an indication of the dynamic range of the ear. LDLs are reduced consistently below 100 dB in patients with hyperacusis. These measurements will aid in the categorisation of patients into category (3) or (4), but will not be sufficient without an appropriate history of sound sensitivity.

It is our practice to obtain further assessment of cochlear function with transient evoked otoacoustic emissions, and distortion products, as well as looking at the fine structure of the audiogram using Békésy audiometry or Audioscan. The rationale for this is the part played by peripheral hearing in certain cases, where tinnitus emerges as a result

of irregularities of cochlear function (the discordant damage hypothesis [1]). This knowledge is important in following the patient's progress, and in using the correct form of directive counselling. Many patients are convinced (and may have been told) that their symptoms are caused by poor Eustachian function, or by other middle ear problems, and they are constantly looking for a simple treatment to get rid of tinnitus. Impedance testing and middle ear reflex measurements shows normal results in over 98% of our tinnitus clinic patients, and will be needed to persuade patients of the correct mechanism, and appropriate treatment by TRT

Teaching – demystification and retraining.

Patients vary in their reaction to tinnitus from mild annoyance, without any particular fears or anxieties, to those who have a classical phobic reaction to it. In many cases the main preoccupation is with the finality, the concept that tinnitus will go on for ever, may get worse, and cannot be effectively treated. These negative mindsets can only be changed by a proper understanding of tinnitus mechanisms; the neurophysiological model. Compliance with a programme that may last 18 months or more will not be achieved unless the patient understands why it is necessary, and also why there is no 'quick fix'. Again the answers that patients need lie in the model. Many patients with mild symptoms are just keen to know what tinnitus is. It is a basic rule of the auditory system, that any new signal must be monitored until it can be identified, and its meaning established. Again TRT is the only treatment that achieves this reliably.

Understanding the auditory system

To understand fully the neurophysiological model, the basics of the auditory system need to be learned. This includes the ear, and transduction process of the cochlea, the concept of tonotopic mapping, and the process of sorting neurally coded frequency information into meaningful patterns before they are perceived in the auditory cortex (Figure 1).

Sub-awareness neuronal networks have several functions:

- pattern recognition;
- memory;
- links with the limbic and autonomic nervous systems.

Appropriate diagrams and the use of simple language, amply illustrated by stories or parables are essential to take patients through this information, regardless of their educational background. For instance the concept of sub-awareness pattern recognition with enhancement or attenuation of signal can be illustrated by the well-known phenomenon of alertness to the sound of first name, as against the habituation to meaningless sounds like the refrigerator, or traffic on a nearby busy road. The develop-

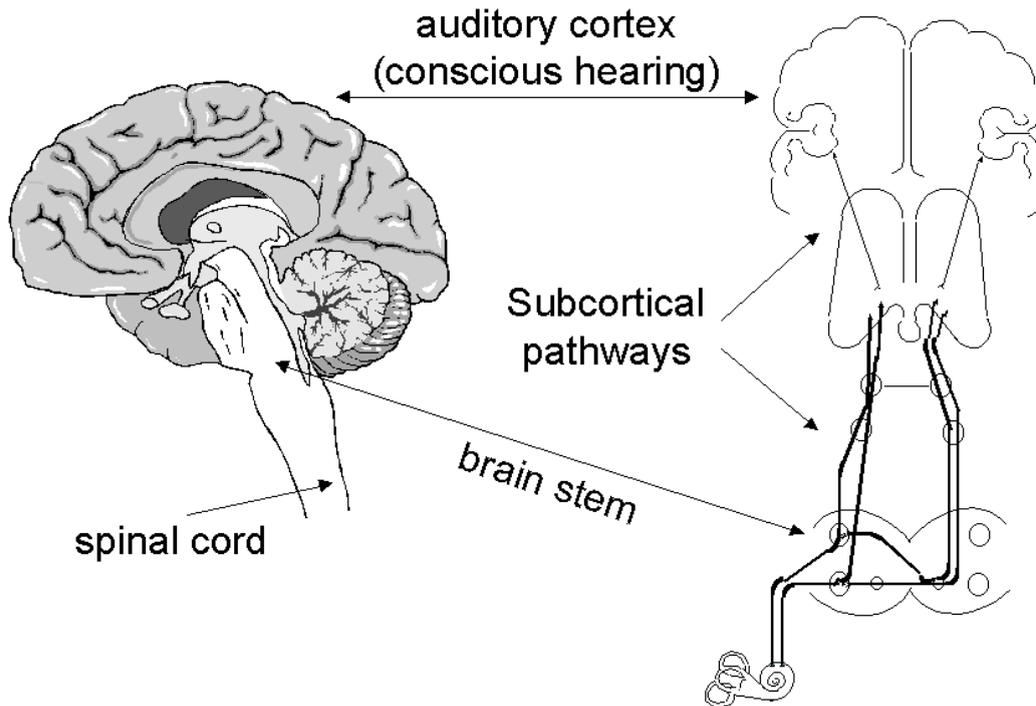


Figure 1 Helping patients understand the importance of auditory perception and sub-awareness processing

ment of these enhancement or suppression effects, take time, and is dependent on a learning process.

Understanding the mechanism of aversive reactions

Pattern recognition plays a vital part in survival and personal security. The reaction to a motor car horn on crossing the road, or a creaking floor-board at night evokes the same limbic and autonomic responses as the sound of a predator to an animal living in the wild. Even a small change in environment, such as elicited by shining a light on an aquatic flat-worm, results in a feeling of annoyance, or

unease, because of a disruption in homeostasis. In each case there is activation of the limbic system to create motivating fear or anger, and autonomic tonal increases to prepare for activity. Once a response has been conditioned it does not habituate, as long as it is concerned with elements of survival (food, procreation or personal security). Identical responses may be generated to harmless elements of our environment because of inappropriate training (e.g. spiders, lifts, aeroplanes and high buildings). Such aversive conditioned responses or reflexes, behave exactly like survival reflexes (Figure 2). They may be generated by any kind of negative reinforcement.

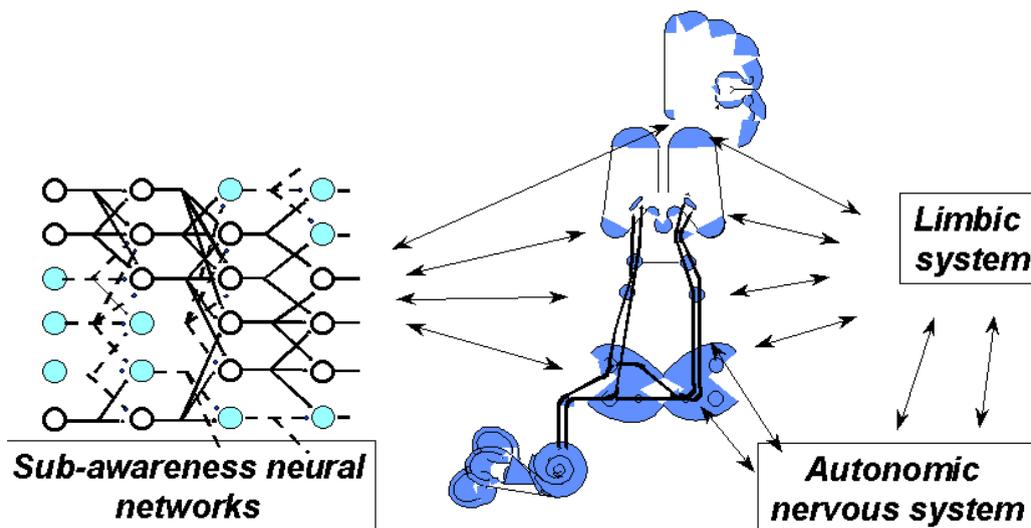


Figure 2 Helping patients understand the relationship of auditory and extra-auditory pathways, and the aversive conditioned reflex

Understanding the Jastreboff neurophysiological model

The various elements relating to tinnitus, its origin, processing of the signal, its first emergence as a perception of sound, and the generation of the aversive conditioned response are explained to the patient using the flow chart (Figure 3).

The principal components involve:

(a) *The source of tinnitus; processing of the signal:*

The source is usually near the periphery of the auditory system, but any neurone in the auditory sub-awareness pathway may contribute to the sounds that are heard. What is perceived at a conscious level is the neural activity present in the highest neurones in this pathway, subsequent to any processing, pattern arranging, enhancement or attenuation that has gone on between ear and brain. In silence, the background activity in the system can be detected easily by almost everyone as shown by Heller and Bergman in 1953 [3]. Where irregularities, even minor ones, of cochlear function exist, these may result in signals which are then imposed on the otherwise random activity of auditory neurones in the absence of sound. The message for the patient being counselled is clear. The source of tinnitus is universal, it is unheard until sub-awareness pattern recognition occurs, and only persists if other criteria are fulfilled.

(b) *Perception and evaluation:* With a knowledge of auditory anatomy and physiology the patient appreciates that sounds are not heard until they reach the auditory cortex. Every new sound has to be evaluated and classified before it may be ignored. The sudden advent of a noise coming from within the head is inherently alarming and understandably leads to a belief that something is wrong. Conventional wisdom about tinnitus is often gained by the patient before its onset, leading to ‘worst fears’

being realised. Subsequently, in a search for help the patient can experience ‘negative counselling’ about the untreatability of tinnitus, its permanence, and the need to ‘put up with it’. Frequently worst fears are not only confirmed, but strongly enhanced. It can be hard work to turn around the thinking of a patient who has received the wrong information from a very eminent colleague. It is worth telling the patient that such information about tinnitus, commonly found in textbooks, is based on a highly skewed population of often phobic tinnitus sufferers, in an era when treatment was largely placebo or ineffective, and before there was accurate idea of tinnitus mechanisms.

(c) *Establishment of the aversive conditioned response:* Once the patient understands the significance of negative evaluation of tinnitus, it can be simply shown by the diagram, that this will inevitably create an aversive response involving an enhancement of limbic and autonomic function. If the evaluation is strongly negative, and fears exist about threatening negative pathology, such as brain tumours or madness, then a strong phobic or aversive reaction can result. On the other hand, only slight, occasional annoyance may result from the loss of homeostasis, or tinnitus being seen as a minor territorial intrusion. Whatever the strength of the reaction, the neurophysiological model applies in every case.

(d) *Vicious circles generated in the conscious and unconscious pathways:* Once an aversive response has been conditioned, several criteria apply:

- The response is ‘set’ in the subconscious, and cannot be ‘turned off’ at will;
- The response will be triggered whenever the signal can be detected;
- The connections are bi-directional and therefore the limbic/autonomic reaction from

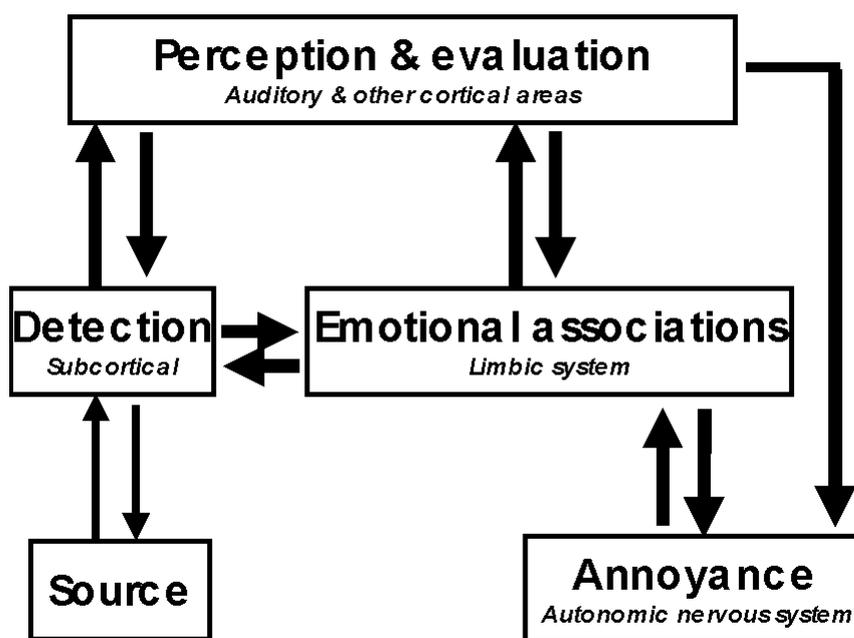


Figure 3 The Jastreboff neurophysiological model

sub-cortical detection of tinnitus enhances the response which in turn enhances detection, and so on, independent of conscious thought;

- Enhanced detection leads to greater perception, and another vicious circle, strengthening the reaction still further. This is the mechanism by which tinnitus perception and reaction can increase without any change in the peripheral auditory system.

(e) *Understanding the difference between emergence and persistence:* It is very difficult for those who have had tinnitus triggered by a strong experience, such as a loud noise, not to feel that the situation is irreversible. It is important to demonstrate how the persistence of tinnitus is dependent on the aversive conditioned response continuing. As the patient will prove, the response can be retrained, and therefore the problem can be solved.

Why this model?

Used in this way, the Jastreboff model can demystify the whole unpleasant experience of the patient's tinnitus. However, once a flaw is found in the explanation, the whole model may be rejected. Therefore the model used with the patient should have the highest degree of compatibility with the physiological processes involved. In 8 years of using the model in this way not a single patient, having understood the model, has been left with an unanswered question. Beforehand it was common place to say 'we just don't know'. It does not make sense to use another model or different illustrations, which have inaccuracies, and which will not satisfy the patient's need for an detailed explanation of their experiences.

Counselling and teaching in different treatment categories

While the basic concepts of auditory function and the neurophysiological model need to be known by everyone, the emphasis may change. In hyperacusis, without tinnitus, (category (3)) the source of the aversive stimulus is outside in the environment, rather than neuronal activity in the brain. However the same process of pattern recognition and enhancement can occur, as with tinnitus. The problem is often compounded by the individual's attempt to block out sound, either by living in very quiet rooms, or with ear plugs or muffs. This leads to further auditory gain and amplification of external sounds, so that when they are heard they are much louder than normal. This is the reason for decreased LDLs. Increasing loudness perception then creates an aversive reaction to the sound. This may be strengthened by worries that sound may be damaging the ear, because it is perceived as being over loud. Discussion about tinnitus sources and processing mechanisms can be left out in this category.

In category (4) patients there is a 'kindling' phenomenon, in which the enhancement of external

sounds, and tinnitus, is made worse by exposure to (normal) environmental sounds, for periods longer than 24 hours, or a good night's sleep. Pathological processes in subcortical auditory pathways are responsible for this phenomenon, which is relatively rare. It creates the hardest-to-treat group, requiring extended treatment both with counselling and sound therapy. Such patients can be made much worse by other therapies involving altered music, and 'pink noise', set to unmonitored levels.

Where phonophobia occurs in category (3), and in almost all patients in category (4), there is a phobic reaction to certain sounds. Percussive sounds are frequently disliked, but traffic sounds, kitchen noises, and even rustling paper can evoke a powerful aversive reaction. Counselling stresses the importance of very gradual reintroduction of these sounds, while reactions are suppressed. It is hard to persuade someone fearful of damage to the ear, with worsening sensitivity, to practise this technique, unless they can understand and believe the model.

Children

Children as young as 4 years have been successfully treated with TRT. The model has to be kept simple, as well as the drawings and parables used to illustrate the child's experience. The parents must be included, as it is often their anxiety about symptoms, rather than the child's, that keeps the reaction going. Children are very compliant about instrument use, easily accept new beliefs and ideas, and because of a high level of brain plasticity (necessarily for TRT to work), improve more quickly than adults and need fewer visits.

Sound therapy – avoidance of silence

The auditory system has developed, in nature, in an environment of continuous background noise. While such nature sounds tend to create a feeling of relaxation, many of the sounds generated by industry, traffic and other machinery, are unwelcome. The ability to isolate our environment from external sound by double window glazing etc. allows much of the day and general all the night-time, to be passed in near silence. This results in abnormal increases in central auditory gain. If a search by pattern recognition processes in the subcortex for external stimuli is unsuccessful, then the sensitivity of detection increases. Consequently when environmental sounds are finally encountered they are unnaturally loud, to the point where they cause distress. The same process of enhancement works with tinnitus pattern recognition, hence the reasons for the Heller and Bergman phenomenon [3]. Patients need to learn by this information, that silence is actually harmful to them, although quietness is not. The environment needs to be enriched with sound on a 24-hour basis, but this must be with sounds that are not themselves likely to create further aversion or dislike. Selecting suitable sounds for enrichment is not a trivial process. Advice such

as 'leave the TV on' is quite inadequate. Nature sounds are best, like moving air (from a fan), water (from a waterfall) or good quality recordings. Music, radio and TV should only be turned on when it is wanted for its own sake. Some of the latest electronic sound enrichment devices work very well. At night enriching sounds must not disturb patient or partner. Night-time enrichment is necessary because the subconscious pathways are active during sleep, and waking with tinnitus (or hyperacusis) at night is much more likely in a silent environment.

The use of earplugs and muffs must be gradually withdrawn and aversive sounds slowly introduced. At no time should any change in sound environment result in a worsening of the patient's reaction to sound. If this occurs then the speed of change is too great. Patients in category (2) (with hearing aids) need to be instructed in the use of sound enrichment, as if they had normal hearing.

Patients in Category (0) have mild symptoms of tinnitus, without a significant aversive reaction. They are given an initial retraining/directive counselling session, with instruction about sound enrichment. They are not fitted with instruments. A follow-up appointment is made for 6 months. Patients who are not improved, or request more help, can be moved into category (1), and formal TRT restarted.

The use of instruments

Wide band noise generators (WNG) which look like are small hearing aids are fitted post-aurally or sometimes in-the-ear. Fitting must be binaural and non-occlusive, to avoid reducing ambient sound. Non-occlusion is important to avoid a reduction in ambient sound resulting in an enhancement of tinnitus perception. This can also temporarily reduce hearing in noise. For this reason post-aural fittings on open moulds are most often recommended. The purpose of wide band noise generators is:

- to enhance background sound, and avoid silence;
- to provide a constant broad band of sound to both ears which is itself quickly habituated;
- to increase plasticity in sub-awareness neuronal networks concerned with pattern recognition, and their connections with limbic and autonomic systems;
- to reduce the impact of tinnitus or aversive external sounds (in hyperacusis) without masking them;
- to reduce gain (amplifying effect) in central auditory pathways.

Broad band noise is preferred as it stimulates auditory neurones regardless of their characteristic frequency and is more easily tolerated and habituated than narrow-band noise. Binaural fitting is necessary to avoid asymmetrical stimulation of the auditory system, which itself can cause tinnitus enhancement. Frequency specific sound therapy is always inappropriate.

Instruments need to be fitted by properly trained audiologists. The method can only be briefly outlined here. WNGs must be comfortable to wear, and the volume control must be sensitive, particularly close to zero.

In category (1) patients, the volume is set close to the 'mixing point' with the tinnitus (Figure 4).

The WNG must never itself produce discomfort or aversion, if this occurs the volume is set too high. It must never alter the perceived characteristics of the tinnitus, although it may reduce its perceived loudness and therefore its impact. It must never mask the tinnitus, as this inhibits habituation, which cannot occur in the absence of the sound-to-be-habituated.

In category (3) patients, the introduction of wide band noise is very gradual, beginning just above threshold and slowly increasing the volume over days or even weeks, to achieve a reduction in abnormal central auditory gain (hyperacusis). Many patients experience some immediate relief of hyperacusis symptoms once instruments are fitted, and ambient sound avoidance with earplugs or muffs has been abandoned.

In category (4) patients, the application of wide band noise has to be even slower, over weeks or months. Failure to do this may result in kindling or 'winding up' of auditory gain, and worsening of symptoms. This is the hardest group to treat, and takes the longest time.

Category (2) patients (significant hearing loss), should be fitted with binaural aids whenever possible and practical. Only 'best practice' fitting will achieve optimal results. Patients must be advised to use sound enrichment at all times.

Retraining exercises

As the aversion to tinnitus is frequently started by classification of tinnitus as a negative event, reclassification or re-evaluation is essential. Frequent reaffirmation of the neurophysiological model, knowledge of the Heller and Bergman phenomenon, and the normality and commonplace of tinnitus emergence, should gradually evoke a different pattern of thinking about tinnitus. It is no longer understood to be a dreaded affliction, but simply 'the music of the brain', and shared by everyone.

It is helpful to spend several short periods of time each day listening to tinnitus (or in the case of hyperacusis, external sounds), without reacting, at first for seconds, later minutes. This is an exercise in diplomacy, in which the concept of tinnitus as an unwelcome guest is gradually changed to one of an old friend. Severely aversive and reactive patients cannot do this to begin with. The professional in charge should carefully monitor this exercise.

Adjunctive therapies

Any treatment, which is effective in reducing autonomic activity, such as relaxation training,

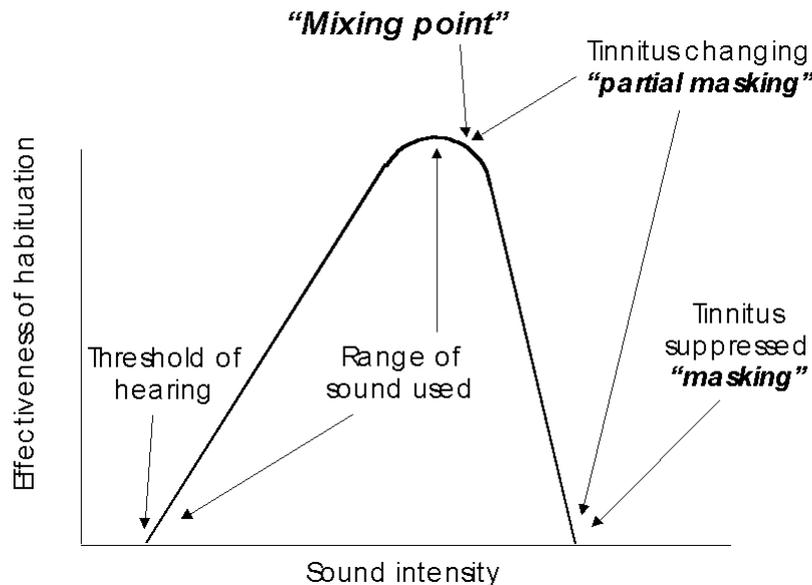


Figure 4 The effectiveness of wide-band noise generators increases as volume is increased towards the mixing point. Once tinnitus is altered or masking begins, effectiveness rapidly reduces

bio-feedback, yoga, and many other alternative therapies, can have a temporary beneficial effect. They work by reducing part of any reactive or aversive process. However they are not specific to tinnitus and hyperacusis, and will not produce a long-term effect unless TRT is applied as well. Relaxation techniques are particularly effective if used in conjunction with the listening exercise described above.

Follow up

Follow up of all patients is essential. In Category (0) patients, one visit is planned to check progress. All categories are advised to come back if a problem recurs. It is advisable to see all severely affected patients one month after the first visit, when doubts about TRT effectiveness can be experienced after initial gains. TRT takes on average 1.5 to 2.5 years to reach a significant and maintained improvement. The number of visits needed varies between 2 and 12. The visits are shared between medical otologist, and audiologist/therapist.

The team

The minimum requirements are for a medically qualified otologist or audiologist, plus an audiologist/therapist able to do instrument fittings, and make measurements. Both should be trained in TRT methods. It is advisable to have access to colleagues in psychology and psychiatry to help with very disturbed patients and other problems apart from tinnitus and hyperacusis that may require treatment. The exact nature and composition of the team will vary according to training and personnel in different departments and in different countries.

Preventative measures

An important part of any TRT program is making all health-care professionals aware of the basic mechanisms of tinnitus and hyperacusis, and to avoid negative counselling, particularly in primary care. Nearly all our patients have either been made worse by inappropriate counselling, or in many cases would not have begun the aversive reaction without receiving negative information about tinnitus. Patient organisations and self-help groups can assist in this process.

Training of professionals

As TRT becomes established, and increasing evidence emerges of its widespread effectiveness compared to other techniques, proper courses need to be established to train those individuals who, in practice, meet tinnitus patients day by day. Experience shows that motivated professionals can learn the basics of TRT in a short intensive course [4], and become effective in using it after 6 months' to 1 year's practice. However, like the practice of audiology itself, the effective management of tinnitus and hyperacusis by TRT can take years to perfect.

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An evaluation of the TRT method

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Tinnitus retraining therapy (TRT) has been in use at the former Royal National Institute for Deaf People Medical Research Unit (RNID MRU) since 1990. This study was undertaken to establish firstly, what the effects of TRT were and whether these effects were sustained over time and secondly, the relative value of the principal components of TRT (directive counselling and sound therapy).

Tinnitus research in general is prone to difficulties in selecting adequate controls, measuring treatment effects and noting the extent of placebo factors. This study was no exception.

In the absence of an adequate control group it is difficult to draw firm conclusions from this study. However the size of response, and the length of time over which this response continued suggests that the individuals in this study were greatly helped with their tinnitus up to 2 years after treatment started. As there was no significant difference in response between individuals who received either directive counselling alone, or directive counselling in addition to various forms of sound therapy, it appears that the most important element of TRT is directive counselling.

Introduction

Evaluating the effectiveness of any treatment for tinnitus is confounded by difficulties in selecting true control groups and in randomising and blinding treatments. In the absence of these elements it is necessary to determine whether the size of the response is such that it is impossible that this effect would be due to anything other than the treatment in question [1]. However measurement of a subjective response has its own inherent limitations. In addition placebo effects are reportedly as high as 40% [2,3]. Whilst they may be a valuable tinnitus treatment in their own right [2,4,5] it is often impossible to differentiate between placebo and treatment effects. Response over time may also be due to spontaneous habituation to tinnitus [6]. Therefore in order to determine the effectiveness of a specific treatment the researcher must know (a) the reliability and specificity of their measurement tools, (b) how much change would have occurred without treatment, and (c) the magnitude of placebo effects. Not always an easy task!

The National Health Service Executive [7] reports three categories of evidence-based medicine. In order of strength these are:

(1) *Randomised controlled studies*. These should include random allocation to either the treat-

ment group or the control group. Ideally the control and treatment groups should have some element of blinding.

(2) *Experimental or observational studies*.

(3) Where categories 1 and 2 are missing, evidence from experts in the field should be used.

The majority of published tinnitus studies, including this one, fall into category (2). Apart from cochlear implantation of profoundly deaf patients, medical and surgical treatments for tinnitus have not so far proved a viable alternative to psychological treatments and sound therapy.

Tinnitus retraining therapy (TRT), and the neurophysiological model on which it is based, have been described in detail elsewhere [8,9,10,11]. In summary there are two principal components, directive counselling and sound therapy. Whilst the exact methods used may have changed slightly, or have differing amounts of emphasis placed on them, they have remained largely similar since described in 1993.

Previous studies have examined the effects of psychological [12,13,14], masking [15,16,17,18], and a combination of psychological and masking therapies for tinnitus. It has been suggested that a combination of cognitive and behavioural therapies used in conjunction with relaxation techniques are more beneficial than either element in isolation [12,13].

There is some evidence that sound therapy in addition to psychological techniques is beneficial, however the exact mechanism is not clear. Several researchers have suggested that sound therapy helps individuals cope with tinnitus [19,20]. Jastreboff

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suggests that sound therapy interferes with sub-cortical detection of tinnitus related neuronal activity by reducing contrast between tinnitus and background neuronal activity, and by reducing central auditory sensitivity [8].

Jakes *et al.* [21] assigned 58 subjects to either: (1) tinnitus masker only, (2) placebo masker (set at a just audible level), (3) cognitive group therapy, (4) cognitive group therapy plus a tinnitus masker or (5) a 2-week waiting list control. They reported few between group differences during the 5-week treatment period, however at the 3-month follow up there was some indication that the effects of cognitive therapy were greater when a tinnitus masker (not the placebo just audible device) was used in conjunction. Patients were also followed up by telephone 1–2 years later, when 46% of individuals who received group cognitive therapy only, in comparison to 10% who received maskers only, reported lasting benefit.

Dineen *et al.* [19] randomly assigned 96 individuals (of which 71 received three months of treatment) to one of 4 conditions: (1) information only, (2) information plus white noise, (3) information plus relaxation training, and (4) information plus relaxation training plus white noise. They reported that individuals who received information plus relaxation training plus white noise reported the greatest improvement overall in coping ability, and the greatest reduction in the Tinnitus Reaction Questionnaire. They also reported that individuals who received white noise reported a greater increase in coping ability than those who did not. The authors concluded that the noise generators influenced the “perception of manageability of tinnitus, rather than modifying the process of tinnitus perception”.

Scott and his co-workers made a similar point. In a study of 3372 patients from 52 centres in Sweden these researchers found that feelings of control over tinnitus and ability to mask tinnitus by external noises were most predictive of whether or not individuals reported increased tolerance to tinnitus and decreased discomfort from tinnitus [20,22]. Lindberg and Scott state that “the importance of emotional control and the more specific external control (maskability) by environmental sounds can be viewed as a control or a coping strategy which the tinnitus sufferer can make use of depending on the situation” [22].

Three TRT studies have been published to date [24,25,26]. None of these have been controlled, and as pointed out by the Wessex report [23] and Wilson *et al.* [14] have major methodological weaknesses.

Jastreboff *et al.* [24] reported that 83% of patients fitted with noise generators, 70% fitted with hearing aids, and 18% of those treated with one session of directive counselling showed significant improvement (set at least 30% improvement in annoyance, percentage awareness, and one area of activity which had previously been affected by tinnitus). Preliminary results from this study [25] suggested that there was little difference in response between

individuals treated with either directive counselling (DC) alone, DC plus just audible noise generators, or DC plus hearing aids.

Sheldrake *et al.* [26] reported the results from 149 patients who had been treated with a mixture of TRT and older masking and partial suppression type approaches. Using a telephone interview and standard questionnaire patients were asked to rate awareness of tinnitus at onset, at the start of treatment, after one year of treatment and at the time of interview. The overall duration of treatment, and the time between the end of treatment and telephone interview varied. In some cases patients had been attending the clinic for up to 15 years. Sheldrake *et al.* Reported that 96.6% of individuals reported improvement, and 19.6% of those who reported improvement reported periods of time when they were unaware of their tinnitus even when “focussing attention on it”. The authors suggest that these results indicate that TRT can totally eliminate tinnitus perception.

The study reported here was carried out by the author and Jonathan Hazell at the former RNID MRU tinnitus clinic in order to establish:

- (1) What the effects of TRT were, and whether these effects were sustained over time;
- (2) The relative value of the principal components of TRT

This paper is presented as a summary of the methods and main results of the study.

Methods

Space does not permit a full description of the directive counselling and sound therapy techniques used, however the reader is referred to references 8, 9 and 10.

Selection of subjects and completion of study

One-hundred-and-eight-six individuals referred to the RNID MRU tinnitus clinic between May 1993 and May 1996 who fulfilled the following inclusion criteria were entered into this study:

- Main complaint of tinnitus, or tinnitus and hearing disability;
- Hyperacusis (if present) not a main complaint;
- Hearing loss (if present) symmetrical and sensori-neural;
- Normal middle ear status;
- No medical, surgical, psychological or masker/noise generator treatment for tinnitus for one year prior to the study;
- Not undergoing medical or surgical management for other otological problems;
- Not undergoing psychological management;
- Able to understand directive counselling in English;
- Able to attend clinic regularly for 12 months;
- Willing to participate in the study.

One-hundred-and-eighty-two of these individuals

received 5 sessions of TRT in a 12-month period, and 159 were followed up 24 months after the start of treatment. Individuals who did not complete the study are accounted for as follows.

Two individuals died in the first 6 months of treatment (deaths were not related to tinnitus), and 2 more were unable to attend clinic regularly. At the 24-month review 9 individuals were unable to attend and there was no response from the remaining 7 despite up to 2 reminder letters. Individuals who did not complete the study were not significantly different from those who did.

Initial assessment and directive counselling

At their initial clinic appointment each individual completed a tinnitus questionnaire before seeing the Otologist.

After completing the questionnaire, the Otologist took a case—history and the individual was referred for audiometric investigations (otoscopy, impedance testing, pure tone audiometry) and tinnitus evaluations (pitch, loudness discomfort level (LDL) and minimum masking sensation level (MMSL) to wide band noise). The same questionnaire, audiometric and tinnitus evaluations were completed after each subsequent treatment session.

After audiometric and tinnitus evaluations were complete, individuals returned to the clinic, and received their first directive counselling session from the Otologist. This consisted of a full explanation of their symptoms in terms of Jastreboff's neurophysiological model.

Allocation to treatment groups

At the end of the session with the Otologist, the Audiologist was informed of the individual's hearing status: NORM (normal hearing = <25 dB HL 250 Hz to 8 kHz); HF (mild high-frequency loss = <25 dB HL 250 Hz to 1 kHz and <70 dB HL 2 kHz to 8 kHz); or MOD/SEV (moderate to severe hearing loss = between 20 dB HL and 80 dB HL 250 Hz to 8 kHz).

The NORM and HF groups were sequentially assigned to receive either directive counselling (DC) only, DC plus just audible noise generators (DC + LLNG), or DC plus high—frequency emphasis hearing aids (DC + HA1). The MOD/SEV group were sequentially assigned to either DC plus hearing aids (DC + HA2) or DC plus combination instruments (DC + COMBI).

After initial analysis of results in February 1995, the DC + LLNG and DC + COMBI sub-groups were discontinued as they were responding less well than the other groups. After discussion with Jastreboff the second phase of the study was started – it was decided that the noise generators were set below optimum level, and so the DC + LLNG sub-group was replaced with DC + noise generators set at, or just below mixing point with tinnitus (DC + HLNG). The DC + COMBI sub-

group was not replaced, and the MOD/SEV group therefore only received DC + HA2. Individuals in the second phase of the study were compared retrospectively to individuals in the first phase. Tinnitus characteristics, and response to directive counselling were similar between the two phases.

This resulted in 5 separate treatment sub-groups, each of which received similar amounts of directive counselling plus/minus various forms of sound therapy. This is summarised in Table 1.

Table 1 Summary of treatment sub-groups, and the hearing status of the individuals they contained

| Group | N | Treatment | Hearing status |
|---------------------------|----|--|----------------|
| DC only (phase 1 & 2) | 54 | DC only | NORM and HF |
| DC + LLNG (phase 1) | 36 | DC + just audible noise generators | NORM and HF |
| DC + HLNG (phase 2) | 36 | DC + noise generators set at, or just below mixing point with tinnitus | NORM and HF |
| DC + HA1 (phase 1 & 2) | 21 | DC + high-frequency emphasis hearing aids | HF |
| DC + HA2 (phase 1 & 2) | 22 | DC + hearing aids | MOD/SEV |
| DC + COMBI (phase 1) | 13 | DC + combination instruments | MOD/SEV |

Timing of treatment and assessment

Individuals were treated and assessed at the following time periods:

- Initial clinic appointment (ST)
Treatment = directive counselling
- One month later (1M)
Treatment = directive counselling and instrument fitting (where necessary)
- Two months later (2M)
Treatment = directive counselling and instrument follow up (where necessary)
- Six months later (6M)
Treatment = as for 3
- Twelve months later (12M)
Treatment = as for 3
- Twenty-four months later (24M)
Treatment = as for 3

Individuals were seen at the start of treatment, 6M, 12M and 24M by Audiological Technicians and Otologists, mainly the second author. All other treatment was carried out by the first author.

Criteria for response

The criteria for response to TRT was set at a 40% or greater improvement after 12 months in two or more of the questionnaire scales ANN, LQ, %AW and LOUD.

Main Results

Change in questionnaire scales during the study

The pre-study period. Median ANN, LQ and %AW at tinnitus onset (rated retrospectively) for ANN, LQ and %AW are shown in Figure 1. Whilst retrospective analysis is notoriously unreliable it gives an indication of whether individuals perceived that their tinnitus had been worsening or not prior to the start of the study. As median tinnitus duration was 5 years, tinnitus onset is noted on the graphs as being 5 years prior to the start of treatment.

The treatment period. Once treatment started the rate of improvement was markedly greater than during the pre-study period. It is noticeable that the greatest improvement occurred after 3 to 6 months of TRT, but continued at a slower rate after 6 months. Between 12 and 24 months after the start of TRT individuals received no further treatment, however %AW and LQ continued to improve, whilst ANN and LOUD remained at a similar level. All changes after 24 months were significant (ANN Friedman (F) $X^2 = 180.336$, $df = 5$, $p < 0.001$; LQ $F X^2 = 194.868$, $df = 5$, $p < 0.001$; LOUD $F X^2 = 109.363$, $df = 5$, $p < 0.001$; %AW $F X^2 = 197.998$, $df = 5$, $p < 0.001$).

Using the criteria of a 40% or greater change in two or more of the questionnaire scales ANN, LQ,

LOUD and %AW, 69.8% of the treatment group responded to TRT after 12 months.

Changes in tinnitus pitch, quality and location during the study

Tinnitus location, quality and number of sounds did not change significantly, however mean tinnitus pitch became significantly lower (ST = 5117 Hz, 12M = 4 664 Hz; $t = 2.36$, $df = 116$, $p = 0.020$).

Changes in minimum masking level and loudness discomfort level

MMSL decreased significantly and LDL increased significantly. These data are presented elsewhere in these Proceedings [27,28].

Differences between treatment sub-groups

Neither the mean change in questionnaire scales, nor the percentage of treatment sub-groups responding to 12 months of TRT were significantly different to that of either the whole treatment group, or other treatment sub-groups. Amongst individuals with normal hearing and mild high-frequency hearing loss individuals in the DC + HLNG sub-group improved more than individuals who received either DC only, or DC + LLNG,

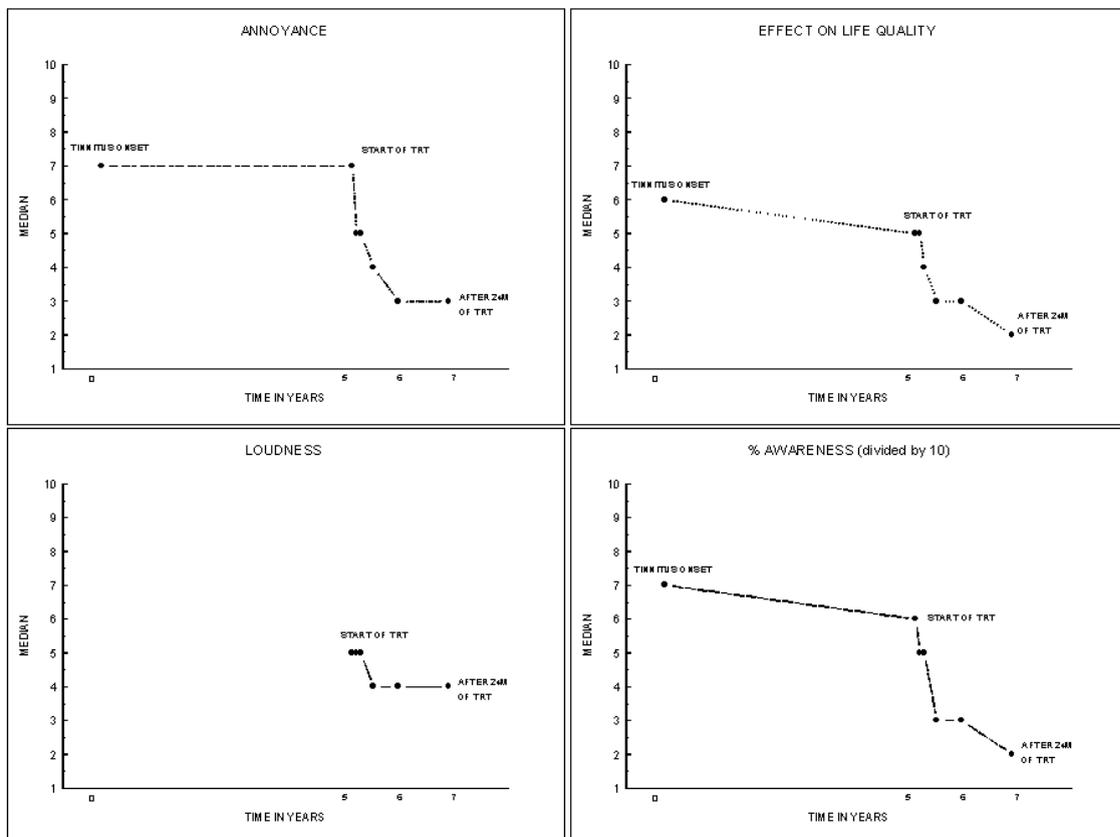


Figure 1 Median ANN, LQ, %AW (divided by 100) and LOUD for the entire TG at the start of treatment (st) and at the time periods 1M, 2M, 6M, 12M and 24M. ANN, LQ and %AW (divided by 10) at tinnitus onset (rated retrospectively at the start of the study) are shown.

Table 2 Percentage of individuals in each treatment group who responded to 12 months of TRT. The hearing status of each treatment group is shown. Criteria for response to TRT was a 40% or greater improvement in two or more questionnaire scales.

| Group | Hearing status | % of group responding |
|--------------|---------------------|-----------------------|
| Entire group | Norm + HF + MOD/SEV | 69.8 |
| DC ONLY | NORM + HF | 72.2 |
| DC + LLNG | NORM + HF | 66.7 |
| DC + HLNG | NORM + HF | 83.3 |
| DC + HA1 | HF | 61.9 |
| DC + HA2 | MOD/SEV | 63.6 |
| DC + COMBI | MOD/SEV | 53.8 |

although differences were not significant. Summary data is presented in Table 2.

Differences in the amount of change in MMSL and LDL after 12 months of TRT were not significantly different between different treatment sub-groups. However for individuals with no significant hearing impairment it appeared that noise generators in addition to either directive counselling or amplification were most effective in reducing auditory sensitivity and MMSL. LDL data are presented elsewhere in these Proceedings (r27), and MMSL data is shown in Figure 2.

Conclusions and summary

In this uncontrolled experimental study neither (a) the reliability and specificity of their measurement tools, (b) how much change would have occurred without treatment, nor (c) the magnitude of placebo effects were known. This means that conclusions regarding the magnitude of response, and whether response was due to TRT or other factors need to be guarded. However some observations regarding points (b) and (c) are made below.

Before the study started the majority of individuals perceived that effect on life quality and percentage awareness had lessened slightly, however annoyance had remained similar. This may indicate the amount of change that would have occurred during the 24-month study without treatment. If changes had continued at a similar rate during the 24-month study as they had done before the study, levels would still have been higher than they were after 12 months of TRT.

It is possible that the majority of the change due to placebo factors occurred at the start of treatment. Particularly at the first interview patients were strongly reassured that treatment would work, and often left this session already feeling better. Even if these changes were due to placebo factors, changes between the start of TRT and 1M indicate how effective these placebo factors are, and confirms

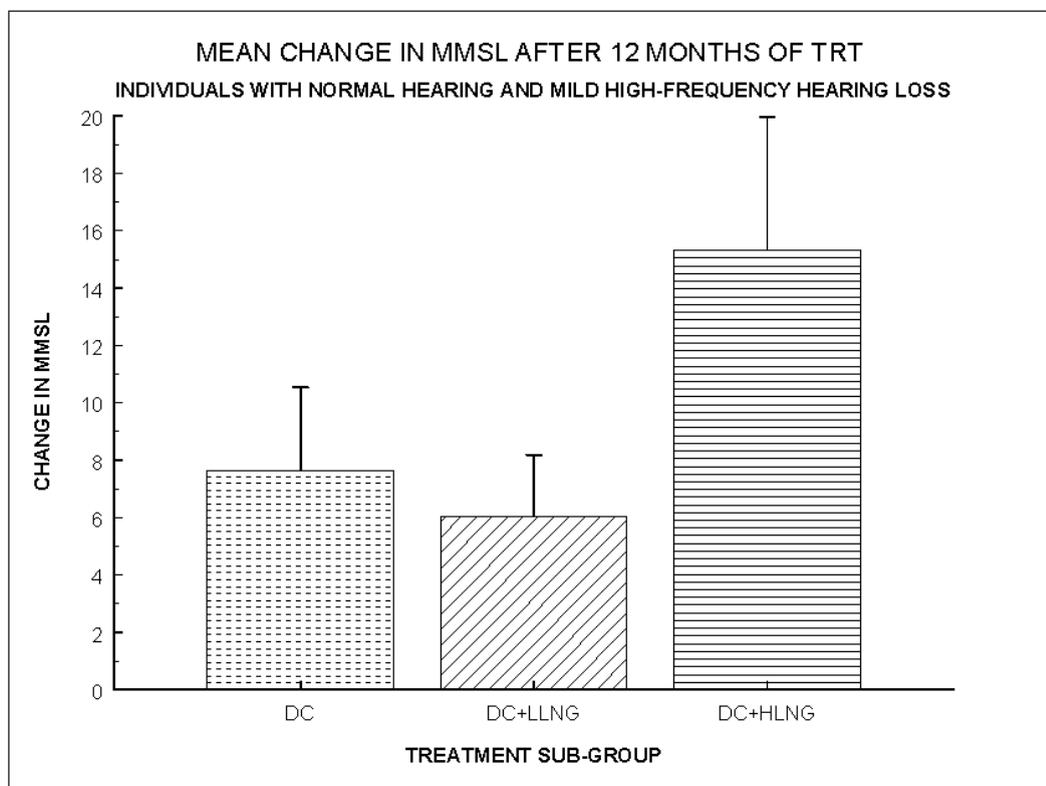


Figure 2 Changes in MMSL after 12 months of TRT for individuals with normal hearing and mild high frequency hearing loss who received either directive counselling (DC) only, DC plus just audible noise generators (LLNG), or DC plus noise generators set at, or just below mixing level with tinnitus (HLNG).

observations made previously that the placebo effect can be harnessed as a treatment effect [2,4,5]. However, if these early results had been solely due to placebo effects, and tinnitus had not continued to improve with further treatment it seems likely that questionnaire scales would have returned to initial levels as placebo effects wore off and patients became disillusioned. In fact, improvements continued up to two years after treatment started.

A second factor which suggests that changes in tinnitus were not solely due to placebo effects is the duration of tinnitus in the treatment group prior to treatment. It has been noted that patients who had depressive symptoms for a shorter period of time are more likely to respond to a placebo treatment than those who had long-standing symptoms [2]. It may be expected from this that patients who had only experienced tinnitus for a short period of time would be more likely to respond to placebo effects. However, the median duration of tinnitus in this study was 5 years.

Two main questions were posed in this study:

- (1) What the effects of TRT were, and whether these effects were sustained over time;
- (2) The relative value of the principal components of TRT.

In answer to the first, individuals who were treated with TRT for 12 months showed significantly lower levels of tinnitus annoyance, effect on life quality, loudness and percentage awareness than at the start of the study. 69.8% of the treatment group showed a 40% or greater reduction in two or more of these questionnaire scales after 12 months of TRT. These improvements were either maintained or continued for a further 12 months without treatment.

After 12 months of TRT, minimum masking sensation level was significantly lower and loudness discomfort levels were significantly higher. These changes support Jastreboff's hypothesis that changes in the strength of tinnitus detection (measured by MMSL) and sensitivity of auditory pathways (measured by LDL) occur with changes in tinnitus reaction and perception.

With the exception of tinnitus pitch, and subjectively rated loudness (which may be influenced by annoyance) the psycho-acoustical qualities of tinnitus did not change significantly.

In answer to the second question, directive counselling appeared to be the most important element of TRT. This is in agreement with previous studies of combination sound therapy and psychological techniques. The gain in wearing any form of instrument in addition to directive counselling appeared to be minimal, and it is therefore likely that directive counselling accounted for the majority of changes seen in tinnitus related annoyance, effect on life quality, loudness and percentage awareness in this study.

For individuals with no significant hearing impairment, changes in questionnaire scales, MMSL and LDL were greatest for the DC + HLNG treatment sub-group, even though these dif-

ferences did not reach significance levels. This may indicate that noise generators set at, or just below mixing point with tinnitus are more effective than either directive counselling alone, or directive counselling plus just audible noise generators. These results are similar to those reported by Jakes *et al.* and suggest that the level of sound therapy is important. This supports Jastreboff's contrast theory [8]. Sound at or just below mixing point with tinnitus would be expected to reduce contrast between TRNA and background neuronal activity more than just audible sound.

In summary, after 12 months of TRT changes in tinnitus reaction, percentage awareness, minimum masking level and loudness discomfort level occurred. The psycho-acoustical qualities of tinnitus remained similar. Tinnitus reaction and percentage awareness were measured after a further 12 months, and changes that had occurred during 12 months of treatment were either maintained, or continued. It is likely that these changes were greater than would be expected solely from placebo effects. The most important element of TRT appeared to be directive counselling, however there was some indication that noise generators set at, or just below mixing point with tinnitus were beneficial.

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Application of TRT in a clinical setting

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This presentation reviews experiences with tinnitus assessment and management by audiologists in a medical center setting. Within a 2-year period, over 250 patients were scheduled for a one hour tinnitus consultation. The main purposes of the consultation, and diagnostic audiologic and tinnitus assessment, were to counsel and educate the patient about their tinnitus, and to develop a treatment program. Approximately one-third of the patient population met criteria and elected to pursue extended TRT (including directive counseling and the use of low level sound devices).

As summarized in Table 1, when compared with all other patients, those enrolling in TRT were more likely to report hyperacusis and depression related to their tinnitus. The TRT group also reported more physician visits for their problem prior to the audiology consult than their non-TRT counterparts. Hearing sensitivity was, on the average, poorer for the non-TRT group, whereas distortion product otoacoustic emission amplitudes were lower for the TRT patients.

Problems associated with long-term treatment in general are, not unexpectedly, encountered in implementing and maintaining a TRT program. In our experience some of these problems are:

- delayed or denied health insurance coverage approval;
- mechanical failure and/or loss of sound devices;
- allergic reaction to devices (itching);
- inconsistent or non-compliance with program requirements;
- premature termination of program;
- potentially related illness during treatment program (e.g. sinus infection);
- unrelated illness during treatment program (e.g., cancer);
- new anxiety and/or stress during program (e.g., health, financial);
- inconsistent follow up visits and/or communication.

Formal assessment of outcome following TRT for this patient series is underway. Meanwhile, our experiences permit several general conclusions. TRT is a viable option for patients with distressing tinnitus. It offers hope to patients who have been inappropriately advised by physicians "there is

nothing we can do for you". In addition, the neurophysiologic model provides a logical and clinically useful framework for the diagnostic evaluation of tinnitus, for appreciating different types of patients, and for patient and family counseling. Finally, components of TRT theory and practice can contribute importantly to the management of most tinnitus patients seeking professional care.

Table 1 Selected characteristics of patients who received an initial consultation alone (72%) versus those (28%) who also enrolled in tinnitus retraining therapy (TRT).

| Characteristic | Consultation | TRT |
|---|--------------|------|
| Age in years | 54.2 | 54.5 |
| Gender | | |
| males | 61.5% | 68% |
| females | 38.5% | 32% |
| Number of physician visits before audiology consult | | |
| 0 | 33% | 7.6% |
| 1 | 39% | 45% |
| 2 | 23% | 21% |
| ≥3 | 5% | 24% |
| Hyperacusis | | |
| no | 47% | 39% |
| yes | 53% | 61% |
| Time since tinnitus onset in years | 9.0 | 11.7 |
| Time aware of tinnitus | 75.3% | 87% |
| Depression | | |
| no | 53% | 31% |
| "blue" | 44% | 51% |
| yes | 3.6% | 18% |
| Number of types of tinnitus per ear | 1.62 | 1.83 |

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Chairman's introduction to Plenary 4: Tinnitus retraining therapy

Tinnitus and the nature of evidence

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The introduction of tinnitus retraining therapy (TRT) [1] has created a tremendous amount of interest and debate amongst professionals, patients and the media alike. Whilst it is heartening to observe this amount of consideration given to tinnitus, it is troubling that at times the discussions have been tinged with acrimony and misunderstanding. With this in mind the aim of this plenary session has been to allow the proponents of TRT to state clearly their model and the clinical method that derives from it, and to consider the present evidence of efficacy.

The need for evidence of a clinical intervention for tinnitus is as strong as that for any other symptom in Otolaryngology and Audiology. Professor Maran, President of the Royal College of Surgeons of Edinburgh, recently discussed the nature of medical evidence [2]. He considered evidence as having various forms:

- religious evidence, based upon faith;
- legal evidence, defined as being "beyond reasonable doubt";
- medical evidence, in the form of randomised, blinded and controlled trials.

Professor Maran acknowledged that in Otolaryngology there is a paucity of this third category of evidence, and that the practice of evidence based medicine (EBM) [4] in Otolaryngology is in its infancy.

What evidence then should we require of TRT? It has been noted that randomised, controlled trials (RCT) are not yet available for TRT [5,6,7] and whilst some further studies have been presented at the 6th International Tinnitus Seminar, these are largely observational, and so do not at the time of writing appear to meet the strict criteria for EBM. In the absence of RCT the practitioner must consider such observational studies, and expert opinion [3] and treat patients as he or she sees fit.

It may be worth striking a note of caution about forming an opinion too early in the development of

a new technique. In 1895 the eminent scientist Lord Kelvin was Master of Peterhouse College, Cambridge. He was asked his opinion of a new physical phenomenon that had caused intense excitement in the scientific community, and indeed among the general public. Lord Kelvin was happy to go on record as saying :

"X-rays will turn out to be a hoax."

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A neuropsychological study of concentration problems in tinnitus patients

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To date there has been only one published study [7] that formally assessed cognitive functioning in tinnitus patients. The results of that study revealed that tinnitus subjects performed more poorly, than controls, on a Letter Cancellation (vigilance) test, but when anxiety was controlled for this difference reduced to a non-significant trend. Non-significant trends for tinnitus subjects to perform more poorly on some other cognitive tests were also observed. The results of that study also indicated that tinnitus subjects reported more difficulties in cognitive functioning on the Cognitive Failures Questionnaire (CFQ) – a measure of general disturbance of cognitive control. The aims of this study were two-fold: (1) to determine whether tinnitus patients performed less well than a control group on more demanding neuropsychological tests of concentration, and (2) to determine differences between tinnitus and control groups would be revealed on the standard tests by a larger subject population. The performance of a group of tinnitus subjects was compared with a control group on a more demanding Letter Cancellation test and on more demanding Verbal Fluency tests than used in the original study. The performance of larger tinnitus and control groups on the standard Verbal Fluency test was also assessed. The groups were also compared on the CFQ. Anxiety, general intellect, age, hearing loss and duration of symptoms were controlled for. The tinnitus group performed more poorly on the more demanding Letter Cancellation test. There were no significant differences on the more demanding Verbal Fluency tests. However, when hearing loss was controlled for the difference in Letter Cancellation scores became non-significant while the difference in Verbal Fluency scores became significant. The same pattern was observed on the standard Verbal Fluency test with larger numbers of subjects. The data from the larger groups of subjects indicated that the tinnitus group reported significantly more problems on the CFQ. It was concluded that tinnitus is associated with difficulties in cognitive functioning but that this is masked by the effects of hearing loss.

Introduction

Problems in cognitive functioning are commonly reported by tinnitus patients [1,2]. There has been no systematic description of these problems has been compiled to date, but tinnitus patients usually refer to the problems in terms of difficulty in concentrating, difficulty reading, or difficulty in following television programmes and other everyday tasks.

It has been commonly assumed that these difficulties reflect the emotional distress associated with tinnitus. It is, however, notable that the relevant questions concerning concentration on published questionnaire measures of tinnitus complaint [3,4,5] load on different factors and not just on the emotional distress factor. It is also the case that the brain areas implicated in tinnitus perception [6] are also involved in cognitive processing. It is therefore

possible that the cognitive difficulties reported by tinnitus sufferers represent changes in neuropsychological functioning that have an organic rather than a functional basis.

To date there has been only one formal study of neuropsychological functioning in tinnitus patients published [7]. That study assessed tinnitus patients on a number of clinical neuropsychology tests. The authors reported that tinnitus subjects performed less well than a control group on a Letter Cancellation task, however this difference was reduced to a non-significant trend when the influences of Trait anxiety and hearing loss were controlled for. There was also a non-significant tendency for tinnitus subjects to perform less well on a number of other tests of cognitive functioning.

There are a number of possible reasons why a statistically significant difference was not observed between the groups on the tests employed in the

earlier study. One possibility is that tinnitus patients' complaints of cognitive difficulties would be apparent only on more demanding tasks. In addition, the number of subjects that took part in the original study may have been too small to show an effect.

As the Letter Cancellation task distinguished the groups in earlier study, this task was selected for further study but in a more demanding form. Among the other tests employed in the original study the clearest trend suggestive of poorer performance by tinnitus subjects was apparent on a Verbal Fluency test ($p = 0.065$). This test was therefore also selected for further study. Modifications of the test that place greater demands on the subject were administered and the original test was also administered to a larger subject sample. It was hypothesised that tinnitus subjects would perform more poorly than a control group on these tests.

Method

Design

This study used an independent groups design with an experimental group (tinnitus group) and a control group (non-tinnitus group).

Subjects

The tinnitus (experimental) group was drawn from patients with tinnitus who were attending the departments of Neuro-Otology and Audiological Rehabilitation within the Royal National Throat Nose and Ear Hospital, London. The control group was drawn from patients attending the same clinics complaining of acquired hearing loss, without tinnitus. The control group was defined in this way in order to minimise the differences, other than tinnitus, between the groups.

All subjects were between the ages of eighteen and sixty years. Only patients who did not have other medical conditions likely to cause cognitive dysfunction (e.g. head injury) were included. Patients taking medication or who had undergone procedures likely to cause cognitive inefficiency (e.g. psychotropic or anticonvulsant medications or ECT) were excluded. Only subjects with hearing that permitted conversation in quiet surroundings were included. Only subjects educated within the British or American school systems were included. These selection criteria were the same as those employed in the earlier study [7]. Twenty-two new subjects formed the tinnitus group and seventeen new subjects formed the control group in this study. In addition, in order to create a larger subject group for some of the analyses, relevant data gathered in the present study were combined with those gathered in the first study [7].

Procedure

Subjects were asked to complete the following questionnaires and tests of cognitive functioning.

Questionnaires: In order to control for the effects of anxiety, subjects completed the Spielberger State-Trait Anxiety Inventory (STAI) [8]. This consists of two lists of 20 questions that the subject answers by ticking a multiple-choice option.

Subjects were also asked to complete the Cognitive Failures Questionnaire (CFQ) [9]. This consists of a list of 25 questions about problems of concentration experienced in everyday life. It has a multiple choice answer system. It is thought to measure a general disturbance of cognitive control.

Neuropsychological tests: In order to control for general intellectual ability, subjects were asked to complete the National Adult Reading Test – Revised Version (NART) [10]. This test is commonly used to provide an estimate of premorbid intellectual ability. The subject is asked to read aloud a list of fifty irregular words used in the English Language. The test is scored in terms of the number of errors of pronunciation; an estimated premorbid IQ may be derived from the error score. The Letter Cancellation test [11]. This assesses sustained attention and vigilance. The subject is presented with an array of letters randomly ordered and tightly printed. The task is to discover and cross out every example of a given letter. The time taken to complete the task is recorded and in this case the number of errors of omission and of non-target letters crossed out is noted. On this occasion a modification of the test was used in order to increase the demands of the task. Subjects were asked to cross out every example of the letter “p” from an array of letters that was twice the size of that used in the original study [7].

Subjects were asked to complete a number of tests of Verbal Fluency. The particular test used was the Controlled Word Association Test [12]; this was used in a standard form and in two modifications designed to make the task more demanding. The standard form requires subjects to say aloud as many words as possible, beginning with a particular letter, within one minute; proper nouns, numbers and word repetition with different suffixes are excluded. This is repeated with two further letters. This form was used in the original study [7]. In the first modification subjects were asked to follow the rules of the standard procedure but using six rather than three letters. The same three letters (C, F and L) used in the previous study were used first, followed by P, R and W. In the second modification subjects were asked to carry out the Verbal Fluency procedure for two minutes duration using a single letter (S). On each occasion the number of acceptable words offered by the subject was recorded.

The level of hearing loss at 250 Hz, 500 Hz, 1 K, 2 K and 4 K as measured using pure tone audiometry was noted from subjects' medical records.

Results

A total of twenty-two new tinnitus subjects and seventeen new control subjects were assessed. The mean age of the Tinnitus group was 45 years (SD =

10.9) and the mean age of the Control group was 38 years (SD = 10.2); the differences in mean ages was not significant.

The control group had their audiological symptoms for a significantly longer period of time ($t = -4.21$; $df = 33$, $p < 0.001$) (Table 1). That group also had significantly poorer hearing for both best ($t = -2.20$; $df = 33$, $p < 0.05$) and worst ($t = -2.70$; $df = 23$, $p < 0.05$) ears (Table 1).

The two groups were closely matched in terms of intellectual ability as measured by the NART (Table 2).

The Tinnitus group obtained significantly higher Trait anxiety scores ($t = 2.74$; $df = 37$, $p < 0.01$) on the STAI (Table 2). There was no significant difference between the groups on State anxiety scores.

Unlike the previous study [7] there was no difference in the mean CFQ scores between groups (Table 2). On this occasion both groups' scores are higher than those observed in earlier study.

The tinnitus group took significantly longer to complete the Letter Cancellation test ($t = 2.11$; $df = 36$, $p < 0.05$) (Table 3) indicating that they had greater difficulty with this test. A Mann Whitney test revealed that there was no difference in the number of errors made by the groups on this test (Table 3).

No significant differences were observed between the performance of the two groups on the standard Verbal Fluency test or on either of the modifications of this test used in this study (Table 4).

As there were significant differences between the groups in terms of hearing loss (for better and worst ears), Trait anxiety, and the time since the onset of symptoms, the data from the cognitive function tests were re-analysed using each of these variables as a separate co-variate.

The difference between groups in the time taken to complete the Letter Cancellation task became non-significant when time since the onset of symptoms acted as a co-variate. This suggests that the shorter time that the Tinnitus group had had their symptoms did affect their performance on this task. The differences in the scores from the Verbal Fluency tests remained non-significant when re-analysed using duration of symptoms as a co-variate.

The differences observed in the cognitive test scores were non-significant when Trait anxiety was used as a co-variate.

When hearing loss in the better ear was used as a co-variate the difference in scores on the standard (3 letter) Verbal Fluency test was significant between groups ($F = 5.382$; $df = 1, 32$, $p < 0.05$) as

Table 1 Duration of symptoms and level of hearing loss.

| | Tinnitus Group | | Control Group | | T | p |
|--------------------|-----------------|-------|---------------|--------|-------|--------|
| | Mean | SD | Mean | SD | | |
| Months since onset | 67.90 | 52.60 | 230.0 | 147.20 | -4.21 | <0.001 |
| | Hearing Loss dB | | | | | |
| Best ear | 25.47 | 22.27 | 46.06 | 31.36 | -2.26 | <0.05 |
| Worst ear | 33.94 | 28.22 | 63.37 | 36.31 | -2.70 | <0.01 |

Table 2 NART, STAI and CFQ scores

| | Tinnitus Group | | Control Group | | T | p |
|--------------------|----------------|------|---------------|------|-------|-------|
| | Mean | SD | Mean | SD | | |
| NART IQ Equivalent | 107.3 | 10.1 | 110.5 | 9.1 | -1.03 | n.s |
| State Anxiety | 40.5 | 11.4 | 34.6 | 8.2 | 1.8 | n.s |
| Trait Anxiety | 46.9 | 11.4 | 37.6 | 9.4 | 2.7 | <0.01 |
| CFQ | 47.7 | 12.2 | 42.1 | 9.24 | 1.61 | n.s |

Table 3 Letter Cancellation Test scores

| | Tinnitus Group | | Control Group | | T | p |
|------------------|----------------|-------|---------------|--------|------|-------|
| | Mean | SD | Mean | SD | | |
| Time | 300.63 | 79.86 | 252.43 | 60.751 | 2.11 | 0.042 |
| Number of errors | 17.54 | 20.65 | 12.00 | 13.46 | 0.94 | n.s. |

Table 4 Scores for the standard Verbal Fluency test and its modifications

| | Tinnitus Group | | Control Group | | T | p |
|-----------|----------------|-------|---------------|-------|-------|------|
| | Mean | SD | Mean | SD | | |
| 3 letters | 37.86 | 13.26 | 42.29 | 12.03 | -1.08 | n.s. |
| 6 letters | 72.68 | 22.58 | 83.237 | 23.18 | -1.43 | n.s. |
| S × 2min | 26.54 | 9.15 | 29.12 | 7.83 | -0.91 | n.s. |

was the difference in the six letter version of the test ($F = 6.823$; $df = 1, 32$, $p < 0.05$). The difference in scores on the two minutes (letter S) Verbal Fluency test and the Letter Cancellation test was non-significant. When hearing loss in the worse ear was used as a co-variate, the differences in scores on the standard (3 letter) Verbal Fluency test became significant ($F = 5.989$; $df = 1, 32$, $p < 0.05$) as did the difference in scores on the six letter version of the test ($F = 7.753$; $df = 1, 32$, $p < 0.01$). The difference in scores on the two minutes (letter S) version of the test emerged as a non-significant trend ($p = 0.074$). The difference in Letter Cancellation test scores was non-significant. These findings suggest that the Tinnitus group had poorer Verbal Fluency test performance but that hearing loss acted to mask this difference between the groups, i.e. hearing loss also contributed to poor performance on these tests.

In order to obtain a larger sample size the data from the standard (3 letter) Verbal Fluency test in this study were combined with those from the same test in the earlier study [7]. In this combined data set there were forty-eight subjects in the tinnitus group and thirty-six in the control group. All subjects were from the same source and the same test procedure was used. The Verbal Fluency data were analysed together with combined data on age, duration of symptoms, hearing loss, the NART the STAI and the CFQ (see Table 5). The two groups were closely matched in terms of intellectual ability as measured on the NART. There was a significant difference between the ages of the two groups; the Tinnitus group was older ($t = 2.08$; $df = 82$, $p = 0.041$).

The control group had their symptoms for a longer period of time ($t = -2.70$; $df = 81$, $p < 0.01$) and had poorer hearing in the better ear ($t = -3.39$; $df = 80$, $p < 0.001$) and in the worse ear ($t = -3.82$; $df = 80$, $p < 0.001$).

The tinnitus group had higher levels of Trait anxiety ($t = 3.82$; $df = 81$, $p < 0.001$) and State anxiety ($t = 2.04$; $df = 82$, $p < 0.05$). The tinnitus group obtained higher scores on the CFQ ($t = 2.58$; $df = 84$, $p < 0.05$). As can be seen from Table 5 there was not a significant difference between the groups in Verbal Fluency test scores.

A discriminant function analysis, using stepwise procedure, was carried out in order to determine

the relative importance of age, duration of symptoms, hearing loss, anxiety and CFQ scores (i.e. the variables on which significant differences were observed) in predicting membership of the groups. This analysis indicated that group membership was predicted by hearing loss in the worst ear ($F = 14.14$; $df = 1, 1$, $p < 0.001$), by Trait anxiety ($F = 12.50$; $df = 1, 2$, $p < 0.001$) and by age ($F = 11.10$; $df = 1, 3$, $p < 0.001$). The remaining variables, i.e. duration of symptoms, hearing loss in the better ear, State anxiety and CFQ did not then predict group membership. While it is hearing loss in the worst rather than the better ear that predicts group membership in this study the importance of hearing loss in this context is again highlighted.

As hearing loss (in the worst ear), Trait anxiety, and age predicted group membership in the discriminant function analysis the data from the Verbal Fluency test were analysed using an analysis of covariance with each of these variables acting as a co-variate. When hearing loss (in the worst ear) was used as a co-variate the difference in the groups' Verbal Fluency scores was significant ($F = 8.274$; $df = 1, 79$, $p < 0.005$) indicating that the Tinnitus group did perform more poorly on this test and that hearing loss was masking this difference. When Trait anxiety was used as a co-variate the difference between the groups' Verbal Fluency scores was non-significant. When age was used as a co-variate the difference in Verbal Fluency scores was significant ($F = 5.304$; $df = 1, 81$, $p < 0.05$) again indicating that the Tinnitus group performed more poorly on the test and that the greater age of that group was masking the difference between the groups' performance on the Verbal Fluency test. These findings suggest that tinnitus subjects do perform more poorly on the Verbal Fluency test.

Discussion

The two groups were comparable in terms of intellectual level as measured by the NART. In the first part of this study the groups were also comparable in terms of age. They were, however, distinguished by the degree of hearing loss; the control group had poorer hearing. The control group also had symptoms for a longer period of time. The tinnitus group

Table 5 Combined data from Studies Four and Five for Verbal Fluency (3 letters), age, duration of symptoms, hearing loss, the NART, the STAI, and the CFQ.

| | Tinnitus Group | | Control Group | | t | P |
|--------------------------|----------------|-------|---------------|--------|-------|--------|
| | Mean | SD | Mean | SD | | |
| Age | 43.62 | 10.63 | 38.72 | 10.78 | 2.08 | <0.05 |
| Months since onset | 65.20 | 60.01 | 131.57 | 135.81 | -2.70 | <0.01 |
| H.L Best ear | 25.50 | 19.51 | 42.72 | 26.51 | -3.39 | <0.001 |
| H.L Worst ear | 33.31 | 24.72 | 56.10 | 29.34 | -3.82 | <0.001 |
| NART IQ | 109.63 | 9.43 | 111.26 | 9.69 | -0.79 | n.s. |
| State anxiety | 38.63 | 10.53 | 34.35 | 8.11 | 2.04 | <0.05 |
| Trait anxiety | 44.91 | 12.04 | 36.23 | 8.72 | 3.82 | <0.001 |
| CFQ | 44.53 | 12.45 | 38.05 | 10.11 | 2.58 | <0.05 |
| Verbal Fluency 3 letters | 31.54 | 12.12 | 36.36 | 12.09 | -1.85 | n.s. |

obtained higher Trait anxiety scores but there was no difference in State anxiety scores.

There was no difference in CFQ scores between the groups in the first part of this study. This is in contrast to the findings of McKenna *et al.* (1995) [7]. The CFQ scores obtained by both groups, and particularly those obtained by the Control group, in this study were higher than those observed in the earlier study [7]. The Control group's CFQ score in the present study was higher than the Tinnitus group's score in original study [7]. These scores indicate that the Control group reported having cognitive problems to the same extent as the Tinnitus group. However, when the data from this study were combined with those from the original study [7] a significant difference in CFQ scores was observed indicating again that the Tinnitus group's perception of greater difficulty in cognitive functioning. In as much as the CFQ is a measure of a "general liability to failure" and of "some deficit of overall control" [9] the present findings indicate that Tinnitus subjects have greater difficulty in this respect. Unexpectedly, the scores also indicate that hearing impairment is associated with compromised cognitive functioning as measured on this questionnaire.

A preliminary analysis of the data from the cognitive tests indicated that the tinnitus group performed more poorly on the Letter Cancellation task; no significant differences were observed on the Verbal Fluency tests. However, the picture that emerges when duration of symptoms, Trait anxiety, and hearing loss are controlled for is different. When duration of symptoms acted as a co-variate the difference in Letter Cancellation scores was non-significant. This suggests that the shorter time that the Tinnitus group had their symptoms affected their performance on this task; it is likely that this reflects a corresponding lower level of adaptation to the symptoms. As in the earlier study [7] when Trait anxiety acted as a co-variate the difference in Letter Cancellation test (time taken) scores was non-significant, again suggesting that performance on this task was also influenced by anxiety levels.

When hearing loss (in the better ear) was used as a co-variate there were significant differences in the Verbal Fluency data, except for the two minute letter S test in which a trend was observed. These findings provide evidence for the hypothesis that tinnitus is associated with impaired cognitive functioning. This pattern of results again points to some difficulty in cognitive functioning associated with hearing impairment. This corroborates the CFQ findings.

Different effects were observed on the two tests of cognitive functioning used in this study, i.e. Letter Cancellation and Verbal Fluency. Both are tests of attention/concentration and poor performance on either may be taken as a deficit in cognitive ability reflecting impaired frontal lobe functioning [11]. There is, however, an important neuropsychological difference between these two tests. Success on the Letter Cancellation task is heavily dependent on

visuo-spatial ability and template matching. The test does have a verbal component in that it requires a minimal knowledge of the alphabet, however, the Verbal Fluency test is much more dependent on verbal abilities and much less dependent on visuo-spatial ability. The present results therefore point to a difficulty in attending to and manipulating verbal information among both groups but significantly more so among the tinnitus group.

The idea that any cognitive deficit might be apparent on more demanding tasks or when larger subject groups is not well supported by these data. The difference in the scores on the six letter Verbal fluency task was more significant (when hearing loss acted as a co-variate) than that for the standard test. It was also the case that the larger data set revealed a more significant difference than the smaller set. However, the fact that a difference was observed on the standard Verbal Fluency test with small subject groups indicates that tinnitus may interfere with the performance of relatively straight forward cognitive tasks and that this is apparent when relatively small groups are studied. This difficulty in Verbal Fluency was apparent only as a trend in the earlier study [7] and was not revealed in terms of a significant difference when hearing loss acted as a co-variate in that study. It is possible that this difference may simply reflect a greater degree of difficulty in cognitive functioning among the subjects in the present study; this is apparent from the CFQ scores.

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The use and predictive value of psychological profiles in helpseeking and non-helpseeking tinnitus sufferers

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In a three-group comparison, a tinnitus help-seeking group (TH) was compared on a number of different psychological measures with a tinnitus non-helpseeking group and matched controls. The TH group showed increased scores on all psychological measures, such as depression, reactions to stress, and anxiety. The results also showed that the TH group had more somatic and cognitive problems, for example in areas as sleep and concentration.

Our hypothesis that tinnitus help seekers are persons with more severe psychological and multi-factorial problems than other subjects with tinnitus, was supported in this study. Consequences for the clinical management of this group is discussed.

Introduction

Why is it that some people tolerate an ongoing continuous tinnitus and some do not? Why does only a small proportion of all tinnitus sufferers persist in seeking help, often trying several more or less effective medical, psychological or alternative treatments over and over again? This group of patients also constitute the main target for clinicians, ENT-specialists and psychologists. Their poor outcome often lead us to believe that this group's problems is representative for the normal course of tinnitus – a phenomena known as “the clinicians illusion” [1]. These patients constitute only about 1–2% of the adult population but suffers from tinnitus to such an extent that their quality of life is seriously afflicted. From a clinical viewpoint one may argue that it is justified to direct most treatment resources towards this group. However, effective treatments should embrace knowledge derived from non-clinical groups, i.e. learning from the majority who does well and cope with their problem. Only recently, arguments against research exclusively focusing on the smaller group of patients not adapting to psychological strain, have been risen [2]. Such arguments can be applied to tinnitus as well, especially since there is a great need for increased psychological and clinical understanding of tinnitus.

We know that approximately 10–15% of the adult population in the western world report tinnitus that is intermittent. In the present study [3], where subgroups from a pool of 2500 randomly chosen Swedes over the age of 18 were included, 15.8% reported tinnitus in accordance with the criteria originally introduced by Coles and co-workers some 20 years ago, later described as Persistent Spontaneous Tinnitus (PST) [4]. This non-clinical sample was compared to a group of patients who had been referred to a specialist clinic due to the severe nature of their problem. All had had various examinations and treatment for tinnitus.

The vast majority of the persons reporting PST handle their complaints well. Based on the research in similar areas where psychological mechanisms have been incorporated in the theoretical framework, Hallam *et al.* [5] outlined a model of habituation for tinnitus. According to this model the normal course of tinnitus is a gradual adaptation with small problems in most acoustic environments.

The tinnitus characteristics in subjects who adapt to tinnitus spontaneously do not differ from those who seek help for their problems. It has been shown that loudness or pitch does not co-vary in any systematic way with the description of annoyance or discomfort [6].

More recently discussed theories of adaptation to tinnitus [7] suggest physiological and respondent conditioning processes acting with tinnitus and its course. Behavioural and cognitive models for coping with stress and chronic illness [8] where subjects own appraisal of control is crucial for favourable outcomes have also been presented. Results from

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research on tinnitus that are in line with the latter framework have been presented earlier [9]. Treatments derived from this stress/coping model have repeatedly been shown to have positive clinical effects for tinnitus [10,11], and similar symptoms [12]. Dimensions of coping like locus of control and self-efficacy, as well as individual differences in psychological factors, are of interest both as predictors for future problems, but perhaps more important as targets for intervention. Accordingly, tinnitus is primarily regarded as a cognitive-behavioural problem rather than a perceptual one. Treatment focusing solely on sensory and physiological habituation to a stimulus would therefore be less prosperous.

From a health psychology perspective, individual differences in psychological factors are predictors of coping capacity and adaptation to tinnitus. Generally speaking trait characteristics, i.e. ones general approach in dealing with the problems of daily life, is a reflection of an individual's constitutional vulnerability. This is especially pronounced in new and threatening situations, like at a sudden onset of tinnitus. For instance, individuals with a pessimistic attribution style are prone to be more vulnerable, use less adaptive coping strategies and have an external locus of control [13]. Consequently they are not able to use their own ability in controlling their problem and are therefore more likely to develop psychological disorders like depression or anxiety.

On the other hand, state characteristics, i.e. psychological responses toward specific problems or situations in life, are more directly related to the individual's present situation. For instance, the covariations between tinnitus, emotional state and external factors are essential. Social support and problem solving skills are also major determinants of how well difficult situations are handled psychologically.

From this psychological point of view any differences in outcome between subgroups are influenced by both naturally occurring variation of stable traits and state-related variation. It is not fully understood which these differentiating psychological characteristics are among subjects who presumably have adapted to their tinnitus compared with those who have not. In the present study [3] helpseekers and non-helpseekers were studied in order to find differences in psychological profiles between groups.

Methods

The three groups studied are presented in Table 1. The first group consist of 117 tinnitus helpseekers with severe problems. The second non-helpseeking group comprise 203 subjects with self-reported PST. No significant between group differences in age or gender were found between those two groups. Each subject was then pair wise matched to a control subject without tinnitus ($n = 320$). As a consequence deviations from expected population levels of the psychological

Table 1 Gender distribution and mean age if two tinnitus samples and matched control subjects.

| | Tinnitus helpseekers ($n = 117$) | Tinnitus non-helpseekers ($n = 203$) | Pairwise matched controls ($n = 320$) |
|----------|------------------------------------|--|---|
| Males | 54% | 57% | 56% (matched) |
| Mean age | 53.9 yrs | 52.6 | 53.4 yrs |
| Females | 46% | 43% | 44% |
| Mean age | 55.7 | 52.1 | 53.0 yrs |

factors becomes possible to calculate in that more valid conclusions can be drawn with regard to the relative severity of complaints in the two tinnitus groups.

The psychological measures used in this study are all established instruments with good psychometric properties. In addition to those, demographic questions and questions of tinnitus and somatic complaints were distributed by mail or by personal contact to the helpseeking group.

Three trait measures were used: (1) the Life Orientation Test (LOT) [13] assessing generalised outcome expectancies and attributional style; (2) the Spielberger Trait Anger Scale (STAS-T) [14]; and (3) the Negative Mood scale (NM) [15].

The five situational state measures used were: (1) the state form of State-Trait Anxiety Inventory (STAI-S) assessing the severity of anxiety [16]; (2) the Daily Hassles scale [17] from which three sub-scales assessing frequency, cumulative severity and intensity (DH-I) are derived (due to the high intercorrelation between those sub-scales and for the sake of clarity, only the latter is presented in this study); and finally (3) the Center for Epidemiological Studies' Depression Scale (CES-D) suitable for measuring depressive state in non-clinical samples [18].

Between group differences in psychological profile were analysed with ANCOVAs (and subsequent post-hoc tests). Tinnitus duration and hearing impairment were used as co-variates since they were the only two demographic variables showing significant between group differences.

Results and discussion

In Figure 1 data from the three samples showed a general tendency for the helpseeking group to have the most profound problems on the trait measures, i.e. LOT, STAS-T and NM ($F = 6.1-10.6$; $p < 0.01$). The state measures STAI-S, DH-I and CES-D were also significantly different ($F = 7.2-25.6$; $p < 0.001$) at a three group comparison. The same relation between groups was also found in the self-reports of problems with sleep ($F = 42.3$; $p < 0.001$) and concentration ($F = 36.6$; $p < 0.001$) – two of the most common psychological consequences reported by tinnitus sufferers.

Post-hoc analyses revealed the unique features in the psychological profile of the clinical sample, i.e. the helpseekers. This group scored significantly higher ($p < 0.001$) than the non-helpseekers and the

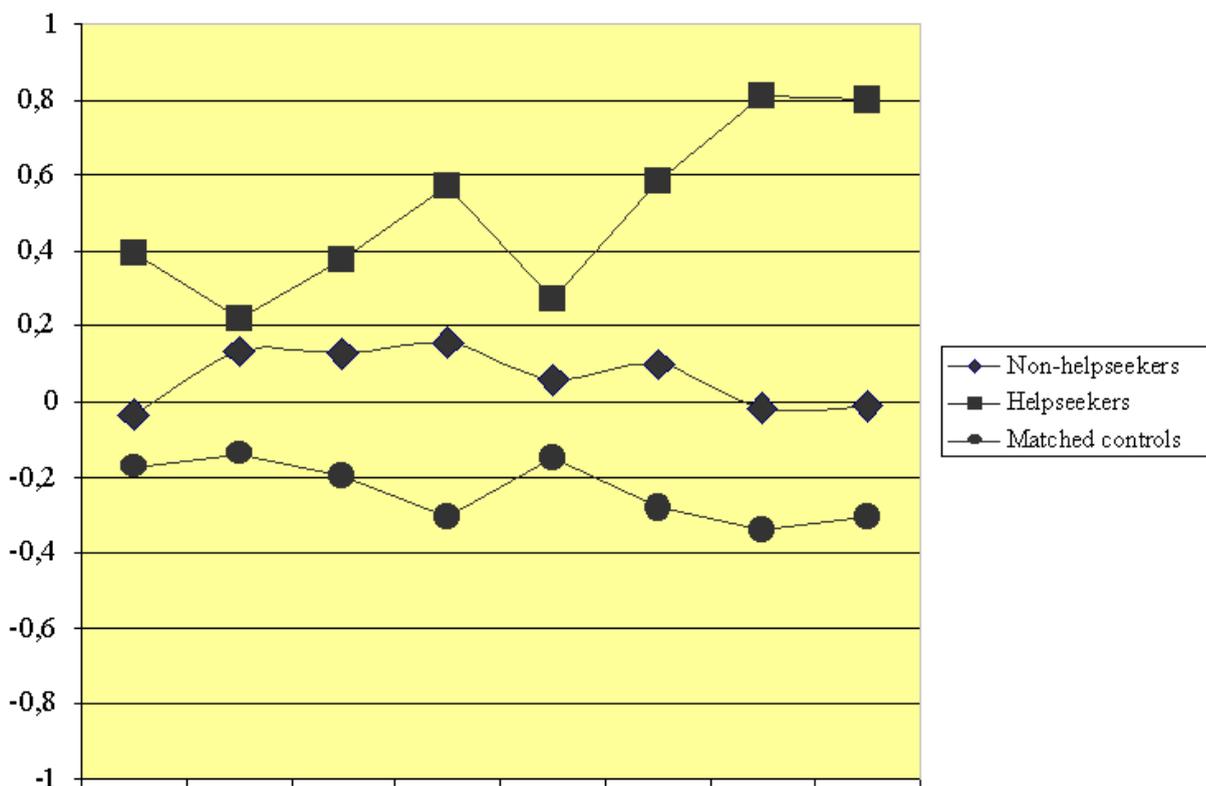


Figure 1 Differences in psychological profile (z-scores) between non-helpseeking, helpseeking tinnitus sufferers and age and gender matched control subjects

controls on the pessimism measure (LOT). They were also more likely to score higher on the reaction to stress and hostility measures than the control subjects. A similar pattern emerged for the state measures where helpseekers fell within the range of clinical depression on the CES—D scale (>16). They were also significantly ($p < .001$) more anxious than the two other groups and rated the intensity of their reaction to everyday problems (DH—I) more severe than others. Finally, this clinical sample reported more problems with sleep and ability to concentrate than the non-helpseekers. Thus, apart from differences in annoyance related to tinnitus, our helpseeking group reported more severe psychological problems, especially problems concerned with negative affect. Such complaints are most likely to render these tinnitus sufferers serious difficulties in successful application of treatments that does not incorporate information of individual differences in psychological profile. Further, their general attributional style could be characterised as more pessimistic, which generally has a positive relation with more passive and non-confronting coping styles [19]. The fact that markers for depressive disorders (sleep and concentration problems) differed in helpseekers as compared with both the other groups bring further support to this notion.

The non-helpseekers reported similar intensity of their tinnitus a psychological profile that differed from the helpseeking group. Further, the non-helpseeking group did not differ markedly from the control subjects in attributional style or in any of the other state or trait. The controls' data may be

regarded as a valid comparison to normal and healthy persons. Psychosomatic complaints scores of sleep and concentration were also closer to the controls than to those of the helpseekers and thus in accordance with normal levels. Thus, this representative sample of non-helpseeking tinnitus sufferers showed a similar psychological profile as did normal control subjects. It suggests that most individuals' psychological resources allow them to cope with tinnitus successfully, and that the non-helpseekers apply adaptive coping skills available to most individuals.

Conclusions

To conclude, data show that the helpseeking group differ significantly from the non-helpseeking group and the control subjects in both trait and state characteristics. Further, in our study the psychosomatic complaints related to tinnitus were more pronounced among helpseekers. It is therefore argued that subjects with a deviating psychological profile have difficulties developing effective coping skills without specific guidance. This is regardless of the tinnitus characteristics, i.e. perceptual qualities of the sound. These subjects would therefore be well suited for cognitive and behavioural interventions in specialised tinnitus clinics. The manner to identify such sub-groups is often a matter of clinical skill. Apart from more general instruments like the ones used in this paper, the inventories specially developed for measuring

different aspects of tinnitus problems should be used more frequently.

Some time ago a psychologist was approached by an otolaryngologist specialising in tinnitus, asking; "Which is the role of the psychologist?". This clinicians' image of a psychologist was that of a professional who talked to and did the counselling with the "tricky cases". However, the answer given was; "A professional who promote cognitive and behaviour change after analysing the individuals assets and problems by means of psychological methods". This paper argues for such an approach by highlighting the importance of psychological factors for the perception of tinnitus, as a basis for analysis and intervention, and as a predictor for outcome. In essence, it should be possible to exploit the natural course of adaptation by studying the psychological characteristics and their relations to that process.

Data in the present study are correlational to its nature, so until evidence of the causal links all conclusions must be cautious. Future work in this area of tinnitus research could focus on prospective outcome studies where treatment aimed at facilitating adaptive coping strategies is tried for the most severely afflicted group. For the patient groups with less deviating psychological profiles more general treatment methods and counselling may be sufficient.

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Cognitive-behavioural therapy for tinnitus-related distress: An experimental evaluation of initial treatment and relapse prevention

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The aim of this paper is to report on the results of a large, dual-site study of the efficacy of cognitive-behaviour therapy (CBT) for reducing distress associated with tinnitus. A sample of 165 distressed tinnitus patients received a standard form of CBT in 8 weekly group sessions in either Sydney or Adelaide, Australia. This treatment was developed following a series of 10 prior studies which had examined the role of non-specific and natural remission factors. Responders to the initial treatment were randomly allocated to either a relapse prevention program, non-specific intervention or no further contact for the subsequent three months, and followed for a further year. Non-responders received further intensive intervention for three months. Initial treatment resulted in a 74% success rate according to specific definitions of clinical response. In contrast to previous studies, these effects were well maintained at the 1-year follow-up. The relapse prevention program did not provide significant advantages over the two control conditions. The high success and maintenance rates are possibly due to the use of highly structured manual-based interventions and detailed patient materials. Non-responders showed only a small additional response to further treatment, suggesting the need for continued research on this group of largely older, more depressed people.

Introduction

Cognitive therapy and relaxation training have emerged as the principal psychological methods of helping people to cope with tinnitus-related distress [1,2]. Cognitive therapy refers to the analysis and modification of behaviours, beliefs, attitudes and attributions. It is based on the cognitive theory of emotions and was first developed by Aaron T. Beck in the late 1960s [3]. Cognitive therapy is one of the most extensively researched psychological therapies and has been successfully applied to a variety of problems including depressed mood, anxiety, anger, marital discord and eating disorders. It has also been found to be effective in helping people manage a range of medical conditions including chronic pain, diabetes, headaches, and cardiovascular problems.

The history of research on cognitive therapy for the management of tinnitus-related distress spans a

period of about 14 years. The aim of treatment is to: (1) help people to use existing skills or acquire new skills to deal with the tinnitus; (2) assist people in ways to use these skills to reduce the emotional distress associated with tinnitus; and (3) lead to a state in which the person either does not notice the tinnitus as often as previously, or reacts less negatively to it over time. Through the process of cognitive restructuring the therapist can equip people with skills to identify and challenge negative beliefs in response to tinnitus. By changing beliefs about tinnitus, the tinnitus will be perceived to be less problematic, and in time, a person may simply not notice the tinnitus because their emotional reaction to it will have been reduced.

There is now a considerable number of published treatment outcome studies on the application of cognitive-behavioural approaches to tinnitus-related distress which include appropriate control groups and adequate measures [e.g., 4,5,6,7,8,9, 10,11]. There are several conclusions that can be derived from this body of research: (1) statistically significant effects are obtained with a variety of cognitive approaches in comparison to non-specific and waiting-list controls [e.g., 4–11]; (2)

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the combination of cognitive restructuring, attention control and relaxation training seems to provide the strongest short-term treatment effects [11]; and (3) the benefits of the most effective interventions cannot be accounted for by the operation of non-specific factors or spontaneous improvement [5]. Thus, there is good evidence to suggest that cognitive-behavioural approaches may produce beneficial effects on reactions to tinnitus, especially when a form of cognitive intervention is employed.

Despite these promising findings two problems have persisted: (1) the rate of response to the combined cognitive/relaxation treatment (using a criterion of clinical response) has been about 50%; and (2) for responders, the clinical effects have not been well maintained at long-term follow-up [e.g. 5,7]. The present study was designed to address these two issues (i.e. to enhance the efficacy of treatment and to reduce the risk of relapse following successful treatment).

Method

Design

The experiment was conducted in two sites (Sydney and Adelaide, Australia). The design of this experiment involved two phases. In Phase 1 a large cohort of people who experienced moderate-severe chronic tinnitus received a standard group program of cognitive-behaviour therapy for tinnitus-related distress. Following conclusion of Phase 1, participants were classified as responders and non-responders. In Phase 2, which commenced three months later, responders to this initial treatment program were randomly allocated to one of three conditions: (1) Relapse Prevention (RP); (2) Group Discussion (GD); or (3) No Further Treatment Control (NFT). Assessments occurred at the beginning of Phase 1 (Pre-Phase 1), end of Phase 1 (Post-Phase 1), the commencement of Phase 2 (Pre-phase 2), end of Phase 2 (Post-Phase 2), and at a 12-month follow-up from the end of Phase 2.

Participants

Participants were recruited through media publicity. One hundred and sixty-five respondents satisfied the following selection criteria: (1) primary complaint of tinnitus of more than 6-months duration; (2) traditional medical and audiological treatments were either not recommended or have failed; (3) previous assessment by both an otolaryngologist and audiologist; (4) at least a moderate degree of tinnitus-related distress as indicated by a score of 17 points or greater on the Tinnitus Reaction Questionnaire (TRQ) [12]; (5) able to speak and read English; (6) willing to participate in a research-oriented management program.

Assessment

Assessment of all participants was conducted via individual interviews and administration of several self-report questionnaires. Interviews were held at pre-treatment and 12-month follow-up. The follow-up interviews were conducted by an independent clinician who was blind to group allocation. The self-report questionnaires were administered at pre-treatment, posttreatment, and at 3- and 12-month follow-ups.

Measures

Tinnitus reaction questionnaire (TRQ). The TRQ is a self-report scale designed to assess the psychological distress associated with tinnitus. The TRQ has been found to possess good psychometric properties such as internal consistency, test-retest reliability, and criterion validity [12].

Tinnitus cognitions questionnaire (TCQ). The TCQ is a 26-item questionnaire designed to assess the types of cognitions that a person might think in response to their tinnitus [13]. The psychometric properties of the TCQ indicate good test-retest reliability ($r = 0.88$) and high internal consistency ($r = 0.91$).

Tinnitus coping strategies questionnaire (TCSQ). The TCSQ is a self-report questionnaire designed to assess a range of cognitive and behavioural coping strategies in response to tinnitus [14]. The TCSQ consists of two subscales which assess the frequency of use of the various coping strategies (TCSQ-Frequency) and benefits derived (TCSQ-Benefits). The psychometric properties of the TCSQ indicate good internal consistency ($\alpha = 0.88$) and test-retest reliability ($r = 0.91$).

Tinnitus effects questionnaire (TEQ). The TEQ (also referred to as the Tinnitus Questionnaire; TQ) is a self-report scale designed to assess dimensions of complaint about tinnitus [15]. The TEQ possesses sound psychometric properties such as internal consistency and criterion validity (Hallam, 1996). The factorial structure of the scale has been replicated by Henry and Wilson [16] and by Hiller and Goebel [17] using a German translation of the TQ.

Beck depression inventory (BDI). The BDI was developed by Beck, Ward, Mendelson, Mock and Erbaugh [18] and has considerable support as a reliable and valid measure of depressive symptomatology [19]. It was employed in the present study as a measure of depressive symptomatology.

Daily monitoring. Participants also completed a daily monitoring form which provided ratings of (1) subjective loudness of the tinnitus, (2) anger or irritability, (3) depressed mood, (4) tension, (5) annoyance, (6) sleep-onset latency, (7) number of awakenings. The monitoring forms were collected over a one-week period on three occasions: (1) between sessions 1 and 2; (2) between sessions 7 and 8; and (3) prior to the 12-month follow-up.

Treatment procedures

Initial treatment (phase 1)

The CBT program was delivered in an intensive format over 8 weekly 2-hour sessions in small groups of 6–8 participants. Two clinical psychologists at each of the two sites conducted the treatment (one therapist per group). The CBT program consisted of basic educational information about the hearing mechanism, the ear, and tinnitus which was provided in the first session. Participants received training in progressive muscle relaxation and were provided with audiotapes of the relaxation procedure to assist them with home practice. Participants also received instruction in a variety of cognitive interventions. Attention control and imagery training are cognitive coping strategies which aim to alter attentional processes through the use of imagery or redirection of attention. Attention control involves a series of practice sessions, aided by tape recordings in which participants attempt to use a number of approaches to divert their attention from the tinnitus to other bodily sensations, images, or external sounds or other stimuli. One example of an imagery exercise is that a person might be asked to imagine that the tinnitus is masked by the sound of a fountain or waterfall. In another exercise, people may be asked to imagine controlling the direction of their attention to and from the tinnitus, perhaps alternating between the tinnitus sensations and the feelings in their feet or hands. The aim of attention control exercises is not just to learn to divert attention, but to help the person to learn that they can control the direction of their attention. Cognitive restructuring involved a detailed analysis of the kinds of thoughts which the person experienced when they noticed their tinnitus, especially when the tinnitus is markedly worse than usual, or when they are distressed. Participants received instruction in developing skills to identify the content of negative automatic thoughts, challenging the validity of negative appraisals, and substituting appropriate and constructive appraisals which are individually tailored. Participants were also provided with training in ‘thought-stopping’ techniques. Participants were asked to complete practice assignments at home during the week in between sessions, and to record their engagement in these practice sessions.

Criteria for response and relapse

Following the initial CBT program (Phase 1), participants were classified as either responders or non-responders to the initial intervention and randomly allocated to receive either (1) RP, (2) group discussion, or (3) no further treatment. Responders were defined as those who (1) obtained a posttreatment score of less than 17 on the TRQ; and (2) displayed a reduction in TRQ scores of at least 50% from pretreatment to posttreatment. These two rules were considered necessary in order to avoid defining participants as responders who show a small

change from just above the criterion for entry into the study to just below the entry criterion (e.g., moving from 19 to 15 on the TRQ). A score below 17 places the subject in the mildly distressed range, and the 50% reduction criterion avoids the difficulty posed above.

Treatment procedures (phase 2)

Relapse prevention (RP). The RP program consisted of several components which were spread over 5 sessions over a 3-month period. The components included: (1) identification of and preparation for high risk situations; (2) generalisation training in cognitive therapy; and (3) lifestyle modification (adapted from Marlatt and Gordon [20] and Wilson [21]). In order to assist participants in implementing the maintenance program, they were provided with a Maintenance Summary workbook in which the key concepts were provided with sections for the entry of individualised details.

Group discussion (GD). Participants randomly allocated to this condition received 5 sessions of non-specific group discussion about tinnitus and its effects, but did not receive instruction in specific relapse-prevention methods. They were encouraged to continue to use the cognitive and relaxation methods as a means of controlling stress and their reactions to tinnitus. The main aim of this treatment was to provide a period which was equivalent in duration and therapist contact to the relapse-prevention program, so that the specific effects of the RP approach could be ascertained.

No further treatment control (NFT). Participants assigned to this condition received no further intervention beyond the initial standard 8-session cognitive-behavioural treatment. They did not receive any training in RP methods. Thus, they served as a comparison group against which any gains in the RP or GD conditions were evaluated by removing any effects due to temporal factors.

Data analysis

Results for Phase 1 (initial CBT program) involved a within-subjects comparison between Pre-Phase 1 and Post-Phase 1. For Phase 2, a series of repeated-measures ANOVAs with between-groups planned contrasts were conducted. The planned contrasts consisted of comparisons between (1) the two ‘active’ treatments: (RP and GD) vs No Treatment (NFT), and (2) RP vs GD. The Time component of the analysis contrasted (1) Pre-Phase 2 vs Post-Phase 2, and (2) Pre-Phase 2 vs 12-month Follow-up. All dependent variables were entered into the analysis. In the case of the daily monitoring, self-ratings of annoyance, depressed mood, tension and anger were combined into a single score (called ‘daily distress’) because the intercorrelations between these variables were very high (0.7–0.8).

Table 1 Means and standard deviations for Phase 1

| | Pre Mean (SD) | Post Mean (SD) | |
|----------------|------------------|-------------------|----------------------|
| TRQ | 36.0 (18.0) | 22.8 (17.0) | 139 138 |
| BDI | 10.8 (7.2) | 7.7 (6.3) | 139 137 |
| TCQ-P | 32.7 (10.4) | 38.1 (8.8) | 130 133 |
| TCQ-N | 24.3 (10.9) | 16.2 (9.7) | 131 137 |
| TCQ-ED | 16.2 (7.5) | 10.9 (6.8) | 139 139 |
| TCSQ | 81.1 (35.3) | 95.5 (34.3) | 90 97 |
| Daily Distress | 1.2 (0.7) | 0.9 (0.6) | 1.1 (0.6) 113 101 90 |
| SOL | 34.9 (27.2) | 29.9 (22.7) | 122 84 |
| Loudness | 2.3 (0.5) | 2.1 (0.5) | 121 102 |
| Nr Awakenings | 1.9 (1.1) | 1.8 (0.9) | 114 81 |

TRQ, $F(1, 136) = 115.25, p < 0.001$; BDI, $F(1, 135) = p < 0.001$;
 TCQ-POS, $F(1, 123) = 38.54, p < 0.001$; TCQ-NEG, $F(1, 128) = 94.47,$
 $p < 0.001$; TQ-ED, $F(1, 137) = 96.73, p < 0.001$; TSCQ, $F(1, 75) = 20.44,$
 $p < 0.001$; Daily Distress, $F(1, 83) = 7.06, p < 0.01$; SOL, $F(1, 77) = 12.40,$
 $p < 0.01$ and Loudness, $F(1, 91) = 6.41, p < 0.013$.

Table 2 Means and standard deviations for dependent for phase 2 and 12-month follow-up

| Measure ¹ | Occasion | Condition | | |
|--|--------------|---------------------------------|-------------------------------|---------------------------|
| | | Relapse Prevention Mean (SD) | Group Discussion Mean (SD) | No Treatment Mean (SD) |
| TRQ | Session 8 | 19.7 (12.7) | 14.7 (8.5) | 16.7 (14.1) |
| | Pre-Phase 2 | 20.8 (13.6) | 17.3 (12.5) | 18.6 (15.0) |
| | Post-Phase 2 | 16.1 (12.2) | 13.5 (8.7) | 13.6 (12.6) |
| | Follow-up | 19.0 (16.7) | 12.5 (7.4) | 18.3 (17.2) |
| TEG-ED | Session 8 | 9.2 (6.3) | 9.3 (4.0) | 9.9 (7.1) |
| | Post-Phase 2 | 5.5 (5.5) | 7.6 (6.4) | 4.2 (5.2) |
| | Follow-up | 7.2 (7.5) | 5.3 (5.2) | 6.8 (8.0) |
| TCQ-POS | Session 8 | 42.6 (6.5) | 37.8 (7.9) | 36.6 (9.1) |
| | Post-Phase 2 | 41.7 (7.4) | 36.0 (10.8) | 33.0 (12.9) |
| | Follow-up | 40.0 (13.9) | 35.5 (11.3) | 32.5 (11.1) |
| TCQ-NEG | Session 8 | 15.2 (9.8) | 13.0 (5.8) | 15.3 (10.2) |
| | Post-Phase 2 | 12.0 (9.7) | 10.5 (6.8) | 12.3 (10.1) |
| | Follow-up | 13.6 (12.2) | 11.4 (6.7) | 12.8 (12.1) |
| BDI | Session 8 | 8.1 (7.7) | 6.9 (3.5) | 5.4 (4.1) |
| | Post-Phase 2 | 8.3 (8.6) | 6.6 (3.7) | 6.6 (9.8) |
| | Follow-up | 8.7 (8.0) | 6.4 (4.8) | 7.0 (7.4) |
| TCSQ | Session 8 | 105.1 (30.3) | 98.1 (31.7) | 83.3 (36.8) |
| | Post-Phase 2 | 99.8 (23.1) | 86.8 (29.4) | 74.3 (36.2) |
| | Follow-up | 86.3 (17.6) | 94.1 (24.6) | 68.3 (38.8) |
| Possibly redo with benefits only note low ns | | | | |
| Loudness | Pre-Phase 1 | 2.3 (0.5) | 2.2 (0.6) | 2.2 (0.4) |
| | Post-Phase 1 | 2.2 (0.6) | 2.0 (0.7) | 2.0 (0.4) |
| | Follow-up | 2.0 (0.4) | 1.9 (0.6) | 2.2 (0.6) |
| Daily Distress | Pre-Phase 1 | 1.1 (0.6) | 1.0 (0.6) | 1.0 (0.6) |
| | Post-Phase 1 | 0.9 (0.7) | 0.8 (0.6) | 0.8 (0.6) |
| | Follow-up | 1.0 (0.4) | 0.9 (0.5) | 1.2 (0.5) |
| Sleep Latency | Pre-Phase 1 | 40.0 (30.0) | 34.7 (25.3) | 33.0 (32.4) |
| | Post-Phase 1 | 32.6 (19.7) | 33.0 (30.2) | 21.4 (18.2) |
| | Follow-up | 22.0 (12.9) | 25.3 (26.3) | 22.1 (16.9) |
| Nr Awake | Pre-Phase 1 | 2.0 (1.2) | 1.7 (1.0) | 1.8 (1.0) |
| | Post-Phase 1 | 1.8 (1.0) | 2.0 (1.0) | 1.3 (0.9) |
| | Follow-up | 1.9 (1.2) | 1.6 (1.4) | 1.5 (0.8) |

¹TRQ = Tinnitus Reaction Questionnaire; TEQ-ED = Tinnitus Effects Questionnaire-Emotional Distress Subscale; TCQ-POS = Tinnitus Cognitions Questionnaire-Positive Subscale; TCQ-NEG = Tinnitus Cognitions Questionnaire-Negative Subscale; TCSQ = Tinnitus Coping Strategies Questionnaire; BDI = Beck Depression Inventory; Nr Awake = Number of awakenings.

Results

Phase 1

Of the 165 participants who commenced treatment, 26 (18.7%) failed to attend at least six of the eight sessions and were therefore counted as discontinuers. A total of 139 participants therefore completed Phase 1 (81.3% of those who commenced).

The within-subjects analysis of the change between Pre-Phase 1 and Post-Phase 1 revealed a significant improvement over time on the following measures: TRQ, $F(1,136) = 115.25$, $p < 0.001$; BDI, $F(1,135) = 47.35$, $p < 0.001$; TCQ-POS, $F(1,123) = 38.54$, $p < 0.001$; TCQ-NEG, $F(1,128) = 94.47$, $p < 0.001$; TQ-ED, $F(1,137) = 96.73$, $p < 0.001$; TSCQ, $F(1,75) = 20.44$, $p < 0.001$; Daily Distress, $F(1, 83) = 7.06$, $p < 0.01$; SOL, $F(1,77) = 12.40$, $p < 0.01$ and Loudness, $F(1,91) = 6.41$, $p < 0.013$. (Different degrees of freedom reflect numbers of participants for whom complete data were available). According to the response criteria, 103 (74.1%) participants were classified as responders following the conclusion of Phase 1 and were offered the opportunity to enter Phase 2.

Phase 2

Of the 103 participants who entered Phase 2, 90 (87%) attended at least 3 sessions and were counted as completers. On the comparisons between conditions, there were no significant differences between the two active treatments and the no treatment control condition in the amount of change between Pre-Phase 2 and Post-Phase 2 on any measure. There were also no significant differences between the RP and the GD conditions in the amount of change between Pre-Phase 2 and Post-Phase 2 on any measure. There was no significant effect for Time.

Discussion

The outcome of the initial CBT intervention for tinnitus-related distress is extremely positive. As a group, the participants displayed significant reductions in means scores on the standard measures of distress which included both the TRQ and the TEQ-Emotional Distress scale. Improvements on these scales were supported by changes on other measures including the BDI, TCQ-POS, TCQ-NEG, TCSQ-Frequency, and daily ratings of distress, sleep onset latency and self-rated loudness. Furthermore, a high percentage of participants reached a relatively conservative criterion of clinical response. The size of effect and the percentage of responders exceeds the results obtained from previous studies conducted by the present authors in this series. The mean posttreatment TEQ-ED and TRQ scores are also lower than those obtained previously, despite similar, if not higher, initial scores. Thus, it can be concluded that the initial CBT treatment produced a substantial clinical impact on distress related to tinnitus. Of course, it may be argued that,

in the absence of a no-treatment control, this effect may be due to natural remission. This explanation seems rather unlikely given the fact that smaller statistical effects have been found in previous studies when CBT was directly compared to waiting-list control conditions [e.g., 5,6,11]. The influence of non-specific factors can probably be ruled out because previous research has also shown significant effects in favour of CBT over a non-specific control condition [5].

The results of the evaluation of the trial of a relapse prevention program for tinnitus-related distress indicated no long-term advantages for this approach. Participants who received the relapse prevention program had no better outcomes, either immediately after its conclusion or at a 12-month follow-up, than participants who received either non-specific group discussion or no further intervention. In attempting to explain this result, consideration needs to be given to the size of the initial treatment effect and the performance of participants in the "no further treatment" condition. The latter condition best approximates the practice of previous trials. In the study reported by Henry and Wilson [5] there was a clear return at the twelve-month follow-up to pretreatment levels on measures of psychological distress associated with tinnitus. In the present study, no such effect was observed. In fact, the participants who received no further intervention after the initial standard CBT program displayed a remarkable stability across subsequent assessment occasions, including the 12-month assessment. It is also important to note that the immediate impact of treatment, as described above, was also unusually large. It therefore appears that the failure of relapse prevention in this study is likely to be due to an unusually potent initial CBT program, rather than a weak relapse prevention program. If the no further treatment group had displayed substantial relapse, there would have been an opportunity to examine whether the relapse prevention program reduced the rate of relapse. It is, of course, gratifying to see that participants who received the initial CBT without any maintenance program in Phase 2 displayed very good results even at the 12-month follow-up point, fully 17 months after the initial treatment session and 14 months after their final therapeutic contact.

The question arises: why was the initial intervention more successful in this study than in previous studies in producing both initial and sustained changes? In the present study, an effort was made to maximise the efficacy of the treatment through a number of procedural modifications to our existing treatment protocol. These modifications were made to ensure that this study was capable of providing a clear evaluation of the efficacy of current "best practice" psychological treatment for tinnitus-related distress. The modifications included the (1) employment of trained therapists, (2) development of a comprehensive highly structured treatment manual, (3) increased focus on structured homework assignments, and (4) production of appropriate written and audiotaped materials to

complement the therapy sessions. In addition, all three treatment components which have been empirically identified to date as contributing to the efficacy of the intervention were included (cognitive restructuring, attentional control and relaxation training). The detailed and comprehensive step-by-step manual was designed to be followed by four separate therapists at the two treatment sites. This procedure was initiated in order to facilitate adherence to a set protocol. It is likely that the strong therapeutic benefits were a result of these various modifications. There has been much interest in the issue of manual-based treatments in recent years. Wilson has suggested that manual-based treatments may produce better outcomes than can be achieved by ostensibly similar treatments without the assistance of a manual [22,23]. It is possible that much of the benefit that has been obtained in the present study may be attributable to the adherence to a detailed therapy manual. Of course, measures of adherence would be needed, together with a design in which participants were randomly assigned to either a manual-based condition or a non-manual-based version of the treatment, in order to investigate the validity of this explanation.

In conclusion, this study has shown that relapse rates might be reducible by paying greater attention to the content and mode of delivery of the initial treatment even without an increase in the standard length of that treatment. Both a high responder rate and a low relapse rate were achieved in this study, but clearly there are people who did not respond or did relapse despite the best efforts being made in both phases of the study to provide a high standard of scientist-practitioner based intervention. A secondary study was conducted to investigate the efficacy of providing more intensive, individualised intervention for those who did not respond to the initial CBT intervention. This study will be the subject of a separate report. It is suggested that further studies on the relapse issue be directed towards the implementation of RP interventions only with individuals who are at high risk for relapse, such as those who are initially more depressed and/or older.

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Effects of psychological treatment for tinnitus: A meta-analytic review

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Meta-analysis is a technique of combining results from different trials in order to obtain estimates of effects across studies. The aim of this paper was to conduct a meta-analysis on psychological treatment for tinnitus. Outcomes of 18 studies including a total of 24 samples and up to 700 subjects were included and coded. Included were studies on cognitive-behavioural treatment, relaxation, hypnosis, biofeedback, educational sessions, and problem solving. Effect sizes for perceived tinnitus loudness, annoyance, negative affect (e.g. depression) and sleep problems were calculated for randomized controlled studies, pre-post design studies and follow-up results. Results showed strong to moderate effects on tinnitus annoyance for controlled studies ($d = 0.86$), pre-post designs ($d = 0.50$) and at follow-up ($d = 0.48$). Results on tinnitus loudness were weaker and disappeared at follow-up. Lower effect sizes were also obtained for measures of negative affect and sleep problems.

Exploratory analyses revealed that cognitive-behavioural treatments were more effective on ratings of annoyance in the controlled studies. It is concluded that psychological treatment for tinnitus is effective, but that aspects such as depression and sleep problems may need to be targeted in future studies.

Introduction

Treatment research on tinnitus is characterized by a lack of consensus and a plethora of different approaches yielding inconsistent results. However, a significant proportion of the controlled studies to date have concerned psychological treatment. These are aimed at decreasing the psychological distress associated with tinnitus, but do not lessen the sound itself [1]. Several psychological treatment approaches have been applied including hypnosis, biofeedback, relaxation training, and cognitive-behavioural approaches combining relaxation techniques and cognitive coping strategies [2]. There have been a few qualitative reviews of the literature on psychological treatment of tinnitus [2–4], but these reviews did not provide a quantitative account of the effects of psychological treatment.

Meta-analysis is a technique of combining results from different trials in order to obtain estimates of effects across studies [5,6]. Further, meta-analysis increases statistical power and can be used to discern differential effects of treatments. Many studies on psychological treatment for tinnitus have been characterized by small samples and low statistical power, hence being suitable for a meta-analysis.

The aim of this paper was to present the results of a meta-analysis on psychological treatment of tinnitus.

Methods

Literature searches were obtained from the databases of Medline and Psychological Abstracts using the key words tinnitus, treatment and psychology. Articles cited in any of the obtained articles were also collected together with articles appearing in journals not yet indexed (e.g. *International Tinnitus Journal*). Conference proceedings and book chapters were excluded. For a study to be included in the meta-analysis, a set of criteria had to be satisfied. The study had to be written in English language and published in a scientific journal. It should present information on number of subjects, interpretable statistics (means and standard deviations), time of measurement, dependent measures, a description of the intervention, and the number of sessions given. For each study, effect sizes were calculated for each treatment modality and outcome category. The effect size is a standardized difference between groups or within groups [7], where differences between means are divided by their common standard deviation. A positive effect size indicates that the treatment group achieved better outcomes than the control group (or posttreatment improved over pretreatment). An effect size of 0.20 is con-

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sidered small, 0.50 is considered medium, and 0.80 is considered large for clinical research [7].

Results

Outcomes of 18 studies including a total of 24 samples and up to 700 subjects were included and coded. Included were studies on cognitive/cognitive-behavioural treatment, relaxation, hypnosis, biofeedback, educational sessions, and problem solving. Effect sizes for perceived tinnitus loudness, tinnitus annoyance, negative affect (e.g. depression) and sleep problems were calculated for randomized controlled, pre-post design, and follow-up studies. Results for the 8 randomized controlled studies are presented in Figure 1.

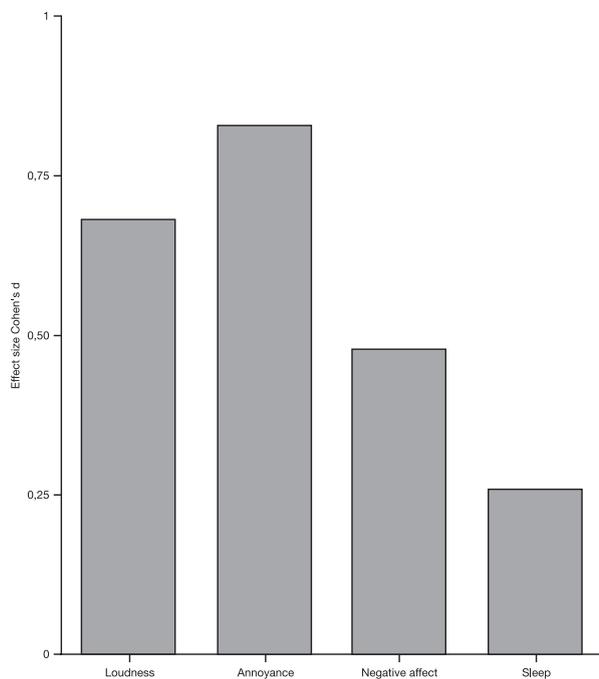


Figure 1 Mean effect sizes (Cohen's d) for randomized controlled studies on psychological treatment for tinnitus. Results on tinnitus loudness, annoyance, negative affect, and sleep are presented.

Effect sizes for pre-post design studies ($N = 18$) are given in Figure 2, and follow-up results ($N = 9$) at a mean follow-up duration of 5.4 months are given in Figure 3.

Overall the results showed strong to moderate effects on tinnitus annoyance for controlled studies ($d = 0.86$), pre-post designs ($d = 0.50$) and follow-up studies ($d = 0.48$). Results on tinnitus loudness were weaker and disappeared at follow-up. Lower effect sizes were also obtained for measures of negative affect and sleep problems. Exploratory analyses revealed that cognitive-behavioural treatments were more effective than other psychological treatments on ratings of annoyance in the controlled studies.

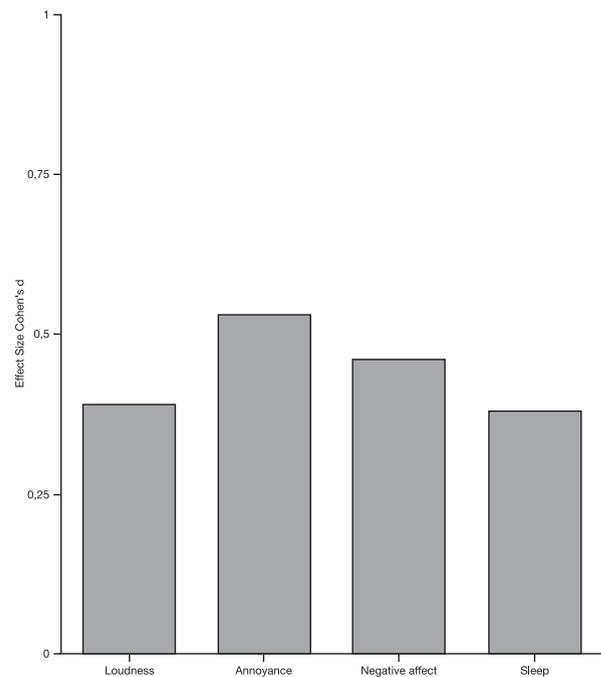


Figure 2 Mean effect sizes (Cohen's d) for pre-post design studies on psychological treatment for tinnitus. Results on tinnitus loudness, annoyance, negative affect, and sleep are presented.

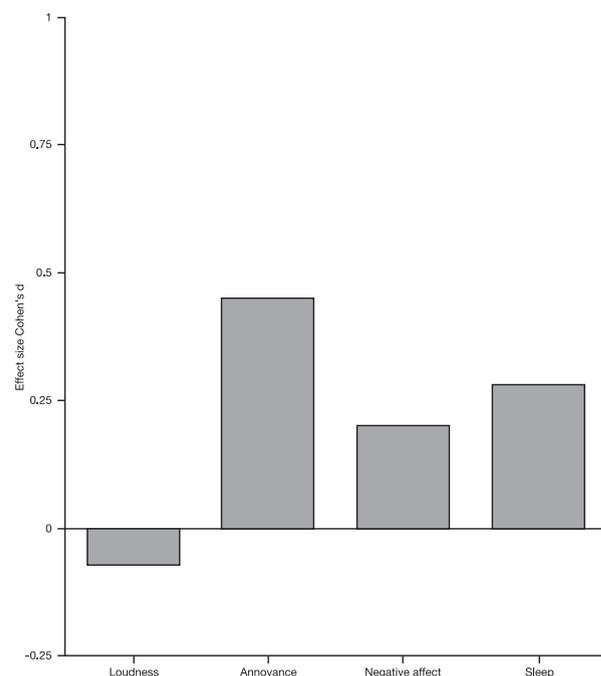


Figure 3 Mean effect sizes (Cohen's d) for follow-up studies on psychological treatment for tinnitus. Mean follow-up duration $M = 5.4$ months. Results on tinnitus loudness, annoyance, negative affect, and sleep are presented.

Discussion and conclusion

The main finding from this meta-analysis was that psychological treatment for tinnitus was found to be more effective than previously asserted in qualita-

tive literature reviews. Effects were most evident on tinnitus annoyance, which also appears to hold in follow-up studies.

Results on ratings of tinnitus loudness showed an effect immediately following treatment in both the controlled design studies and in studies using within-subject designs. However, at follow-up the effects were not sustained, which may imply that perceived loudness is not targeted enough by psychological treatment or that the effects only are brief and short lived.

The meta-analytic results on tinnitus annoyance were more positive. The effect size for controlled designs averaged 0.86, and for pre-post comparisons the effect was 0.50, and at follow-up 0.48. Judging from this analysis, annoyance is decreased following psychological treatment. This was an expected finding since annoyance typically is addressed in psychological treatment of tinnitus [8].

Results were also calculated for ratings of negative affect, which is a summary term for negative experiences such as anxiety and depression. We expected that positive effects would be found on ratings of negative affect, but the effects found were weaker than those for tinnitus annoyance. It is possible that emotional factors such as depression may need to be targeted separately in psychological treatments of tinnitus distress.

We calculated effect sizes for treatment effects on sleep disturbance caused by tinnitus since this is a highly salient negative consequence of severe tinnitus. In our clinic 70% of the patients report sleep problems [9]. Although the results in this meta-analysis were promising, the effects found were weak. Given that effective behavioural interventions have been developed for sleep disturbance, it is somewhat surprising that these have not been used more consistently in tinnitus treatment research. A possible cause may be that so many treatment ingredients need to be included and that the number of sessions usually are restricted.

The effect sizes obtained in this meta-analysis are not negligible and in fact the effect size found on annoyance in the controlled trials (0.86) counts as a large effect [7]. An effect size of this magnitude can be interpreted as showing that the average treated subject has a rating of annoyance lower than 80% of the untreated subjects. Although we found some support for the notion that psychological treatment has long term effects, additional follow-up studies are needed since only a few could be located for this

meta-analysis. Further, the average follow-up period in this meta-analysis was no longer than 5.4 months.

Standard of reporting results was sometimes extremely low, which works against accumulated knowledge by means of systematic meta-analytic reviews. This leads to the recommendation that tinnitus researchers presents means and standard deviations in their reports and that they become clearer when describing their treatment components.

Finally, we end this meta-analytic review with the hope that systematic meta-analytic reviews will become more common in audiological research. Meta-analysis provides an indispensable technique to integrate bodies of literature where single studies often fail to provide any generality of findings.

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Hyperacusis assessment: Relationships with tinnitus

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Clinical hyperacusis consists in a marked intolerance to ordinary environmental sounds while hearing thresholds are normal. The incidence of hyperacusis in individuals with tinnitus has been reported to be as high as 40–45%. Moreover, it seems that a peripheral auditory system, the medial olivo-cochlear system is less efficient among patients with tinnitus and in one case of hyperacusis subject. The aim of our study was then to explore this efferent system functioning in hyperacusis patients with no other pathology like tinnitus to study the involvement of those fibers in auditory hypersensitivity itself. Hyperacusis individuals have been isolated according to patient self-report. Psychoacoustical tests: loudness discomfort level measurements and loudness growth assessments were performed to quantify their auditory hypersensitivity. Auditory dynamic range were lower in hyperacusis than in control subjects. The medial olivo-cochlear system appeared to be more efficient in control than in hyperacusis subjects, but this tendency was not systematic. A peripheral auditory deficit could then occur in hyperacusis, and may be could reflect more central auditory dysfunctioning.

Introduction

Many authors have tried to define the pathological auditory hypersensitivity usually called hyperacusis, but there is no universal agreement with respect to definition, assessment or interpretation of hyperacusis test data [1]. Hyperacusis is also known as phonophobia and dysacusis [2]. Hyperacusis as defined here is a relatively rare disorder about which little is understood, but it can be quite devastating to the patient. It is a subjective phenomenon and cannot be verified or quantified by objective measurement just as tinnitus cannot usually be objectively verified. It can only be described through patient report. Reported characteristics and symptoms of hyperacusis are varied according to each patient. Jepsen [3] stated that hyperacusis is more often an abnormal sense of discomfort evoked by sounds far above the threshold of hearing, called phonophobia; this is presently referred to as suprathreshold hyperacusis. Vernon [4] stated that clinical hyperacusis is a person's marked intolerance to ordinary environmental sound when, in fact, hearing thresholds are normal; this latter statement is consistent with the present definition of suprathreshold hyperacusis. There is an absence of attempting to identify types of hyperacusis and few attempts to establish its clinical significance. In the history

interview, the patient is asked several questions related to sensitivity to sound i.e. hyperacusis. The answers are considered a self-report, that is a subjective report of the presence/absence of hypersensitivity to sound. Hazell and Sheldrake [5] noted that sound intolerance may be part of a global sensitivity, including bright lights and tactile stimulation. Hyperacusis may be peripheral (middle ear or cochlea) in origin or systemic (central or emotional) in origin.

In spite of the difficulty encountered clinically in attempting to diagnose the subjective complaint of hyperacusis, it seems that hyperacusis can be identified by the loudness discomfort level test and the auditory dynamic range [6].

Vernon [4] reported that desensitization could be achieved using low-level masking. The data of Hazell and Sheldrake [5] support this hypothesis in a larger group, and show for the first time that tinnitus maskers may reduce measured loudness discomfort levels significantly, as well as symptomatic hyperacusis. The clinical goal was to remove tinnitus perception from the patient's consciousness, and to initiate and facilitate the process of tinnitus habituation. These data could be explained by an abnormal central auditory gain, which might result in enhanced perception not only of external sounds (resulting in hyperacusis) but also of tinnitus. The clinical effectiveness of white noise masking in both hyperacusis and tinnitus may in part be due to a reduction in gain in the auditory system mediated through the auditory efferent system [5] which may well be implicated

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in the interaction between peripheral and central hearing function [7,8].

Hyperacusis is often accompanied by tinnitus. The incidence of hyperacusis in individuals with tinnitus has even been reported as high as 40–45% [9] or 20.1% in 628 chronic tinnitus sufferers. It was then suggested that hyperacusis could be regarded as a pretinnitus state [10].

It seems however, that the peripheral auditory system could be involved in the generation of tinnitus [11]. This hypothesis was supported by the fact that the tinnitus is generally localized on the side where the amplitude of otoacoustic emissions, representing the micromechanical active properties of the cochlea, is lowest [12], and by the fact that the medial olivo-cochlear (MOC) system modulating these active mechanisms is reported to be less efficient on the side of the tinnitus (in patients suffering from unilateral tinnitus) than on the other [13,14]. The MOC function has also been reported to be altered in a case of hyperacusis [15]. Given the possible links between tinnitus and hyperacusis, it is justifiable to verify whether the auditory periphery system could be involved in hyperacusis.

The aim of this study was then to explore MOC function and transiently evoked otoacoustic emissions in hyperacusis subjects, to test peripheral auditory system involvement in this pathology as it has been done in patients with tinnitus.

Moreover, to quantify hyperacusis, auditory dynamic ranges were measured since this test was relatively successfully employed for hyperacusis assessment [6]. As loudness seems to be the basis of judged annoyance and noisiness [16], a loudness assessment test could permit to quantify hyperacusis, at various intensities. Then, another test complementary [17] has been used to quantify hyperacusis.

Material and Methods

Subjects

Hyperacusis subjects were selected according to the following criteria: no known hearing impairment such as hearing loss; report of auditory hypersensitivity to ordinary environmental sounds altering quality of life.

It was not obvious to find those subjects since most of hyperacusis patients also suffer from other pathology such as hearing loss, tinnitus, facial palsy, autism, . . . However, 14 hyperacusis subjects (with no other pathology) including 11 females and 3 males aged from 14 to 49 years (mean age = 32.4; standard error (SE) = 3.03) have been identified and were compared to 14 controls of the same sex and averaged age, from 13 to 58 years (mean age = 33.3; SE = 3.8) including 11 females and 3 males.

Auditory dynamic range

The ADR is the difference between the absolute pure tone threshold i.e. the minimum detectable level of a sound in absence of any other external

sounds, and the loudness discomfort level corresponding to the intensity at which the sound was considered as uncomfortable to the ear, not just loud [6]. To calculate ADR, firstly, the auditory thresholds were determined for each subject and secondly, loudness discomfort level were measured. The gap between these two limits constitute the ADR.

Tonal audiometry was conducted using a diagnostic audiometer (model AD 28) and telephonics model TDH 39 earphones to measure pure tone thresholds at various frequencies in the following order, 0.25, 0.5, 1, 2, 4 and 8 kHz, in a single session using monaural presentation. All the pure tones were of 500 ms duration time, for full threshold power integration. Both ears were tested, in a random order. A variant of the psychophysical method of limits was employed. The tone level was initially set at 30 dB HL and decreased in 5-dB steps until the subject reported being unable to hear the tone; it was then increased in 5-dB steps until the subject started to hear the tone again. This descending and ascending approach to absolute threshold was performed until stability was reached, i.e. three identical responses given in succession.

Loudness discomfort levels were obtained for each ear individually at the same frequencies that pure tone threshold and using also a method of limits, but simplified to avoid listening too much to loud tones. The subjects were instructed to indicate when the sound delivered through the earphone became uncomfortable to the ear as if they were watching television and that the sound was loud so much so that they wanted to turn down the volume. Loudness discomfort level judgements were made based on an ascending presentation method by 5-dB steps from 45 dB HL. Two trials were used for each loudness measure and permit to calculate an averaged value of ADR to ensure reliability.

Loudness growth assessment: the LGOB test

A procedure similar to a current test called loudness growth per $\frac{1}{2}$ octave band (LGOB) described by Allen *et al.* [17] was employed, except that in this method, loudness could be assessed using six different ratings, and 5 different frequencies. In our method, in order to avoid repetitions of loud sounds, the procedure was simplified by using five ratings and one frequency, a 1 kHz pure tone. When the subjects heard monaurally a sound, through the TDH 39 earphones delivered by the Diagnostic Audiometer AD 28, they had to assess the tone loudness by describing it using the terms: “very soft” quoted 1 “soft” quoted 2, “normal or comfortable” quoted 3, “loud” quoted 4 and “too loud or uncomfortable” quoted 5. If the subject failed to respond to the stimulus presentation, it was given the value 0, indicating the threshold. During the first phase procedure, the subject estimated the upper and lower bounds of the intensity used for testing, and simultaneously obtained practice on the task. The second phase is data collection with randomized presentations of the various intensities

in multiples of 5-dB in the dynamic range. Each intensity was presented 3 times during the test except when the subject responded "too loud". There was only two occurrences of a "too loud" sound and after each, the subjects were given few extra seconds to recover. For each rating of the loudness, the corresponding averaged intensity was calculated using the scale described above. The results were represented by a loudness growth curve.

TEOAE recording and assessment of MOC system functioning

EOAEs were recorded using the ILO88 Otdynamics system, described in detail by Kemp *et al.* [18], which consists in measuring ear-canal sound pressure variations following a transient acoustic stimulation. The stimulation was unfiltered clicks created by 80 μ sec direct-current pulses, presented at a rate of 50 Hz, at five different sound pressure levels, ranging from 59 to 71 dB SPL intrameatal in 3 dB steps, presented in a random order. EOAE amplitudes were recorded in both ears, using the linear method, in presence and in absence of a contralateral broad-band noise stimulus of 35 dB SL activating the medial efferent system. The analysis time was 20 ms, the first 3.0 ms being eliminated. To assess MOC feedback in the groups, equivalent attenuation was calculated [12], as the attenuation of ipsilateral stimulation equivalent to the effect on EOAE amplitude observed with the 30 dB SL white noise contralateral stimulation.

TEOAE were also measured in response to 80 dB SPL unfiltered clicks using the linear method, in absence of contralateral acoustic stimulation, in order to test the difference of TEOAE amplitude between hyperacusic and non hyperacusic subjects.

Results

Tonal audiometry

A three-way repeated measures (RM) ANOVA with factors group (hyperacusic and controls), ear (right and left ear) and frequency has shown no hearing threshold difference between hyperacusic and non-hyperacusic subjects whatever the ear and the pure tone frequency considered ($p > 0.05$).

Objective measurements: TEOAE and MOC system functioning

As represented in Figure 1, TEOAE amplitudes seem to be lower in the left than in the right ear and in controls than in hyperacusic patients. A two-way RM ANOVA only confirmed the interaural difference ($F(1,26) = 5.75, p < 0.05$), but did not show any statistically significant difference of TEOAE amplitude between the two samples as well in the right than in the left ear ($p > 0.05$).

A two-way RM ANOVA performed on equivalent attenuation values representing MOC system functioning failed to find significant difference of

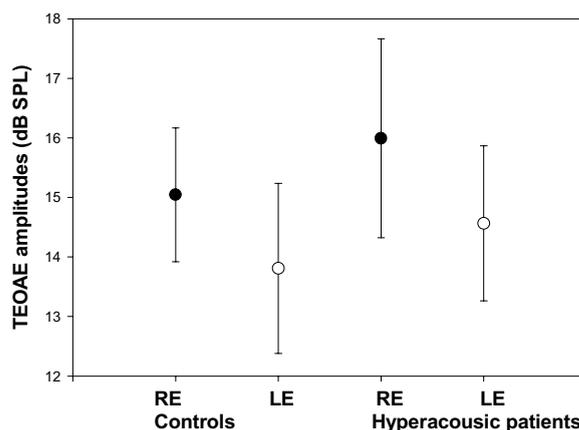


Figure 1 Means and standard error bars of TEOAE amplitudes in both the right (RE) and the left (LE) ears of hyperacusic and non hyperacusic subjects.

these values between ears and between hyperacusic and control subjects. However, in Figure 2, there was a tendency for right ear equivalent attenuation to be lower in controls than in hyperacusic patients.

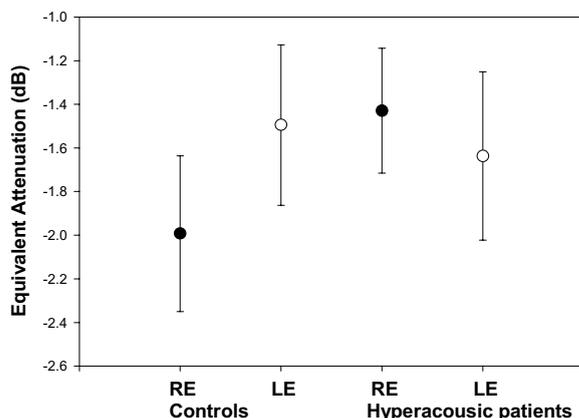


Figure 2 Means and standard error bars of equivalent attenuation (representing contralateral acoustic stimulation) in both the right (RE) and the left (LE) ears of hyperacusic and non hyperacusic patients.

Psychoacoustical tests: ADR and LGOB

As illustrated in Figure 3, ADR appear to be higher in controls than in hyperacusic subjects, in both ears. However, a three-way RM ANOVA considering the factors ear, frequency and population did not show a statistically significant difference of ADR between hyperacusic and nonhyperacusic subjects, whatever the ear and the frequency considered ($p > 0.05$).

In Figure 4, loudness growth curves are represented for both ears of the two population samples studied. For intensities higher than 50 dB HL, the 1 kHz pure tone was perceived louder by hyperacusic patients than by their controls. A three-way RM ANOVA confirmed this tendency given that loudness assessment was statistically significantly different between the hyperacusic and nonhyperacusic subjects according to the sound qualification ($F(5,130) = 6.12, p < 0.0001$).

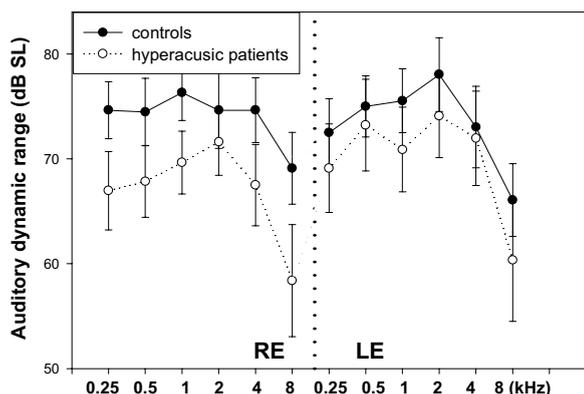


Figure 3 Means and standard error bars of auditory dynamic range in both the right (RE) and the left (LE) ears of hyperacusis and non hyperacusis subjects.

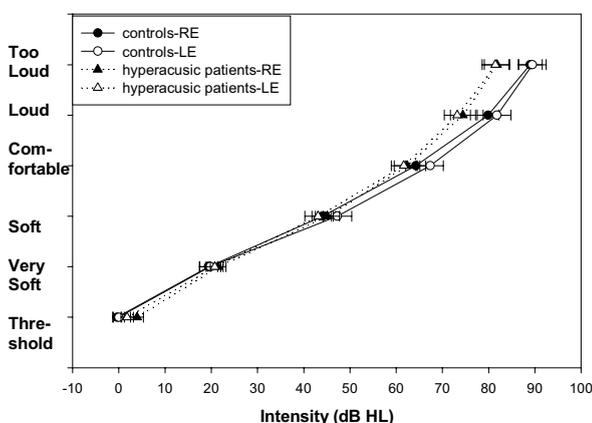


Figure 4 Means and standard error bars of the 1-kHz pure tone intensity for each loudness qualification in both the right (RE) and the left (LE) ears of hyperacusis and control subjects. All these averaged values constitute the loudness growth curves of the LGOB test.

Discussion and Conclusion

Peripheral auditory system involvement in hyperacusis

Contrary to patients with tinnitus showing less functional MOC system in the ear ipsilateral to tinnitus [14], the MOC system has not been found to be less efficient in hyperacusis than in non hyperacusis subjects. However, a tendency for a more inhibitory activity of the MOC system was noticed in Figure 2, and could become significant with more hyperacusis subjects. The interindividual variability in hyperacusis patients of auditory manifestation and of hyperacusis aetiology could explain the absence of a clear and statistically significant result. It could also be that the MOC system is only involved in hyperacusis with a peripheral origin such as the one hyperacusis case of a previous study [15]. However, even if hyperacusis has a central aetiology, the MOC system could intervene in hyperacusis since it is involved in feedback loops including peripheral and central auditory structures [19].

Maybe it should be distinguished between hyperacusis patients the various origins and manifestations of this pathology, to better analyze our results. Indeed, as the MOC is known to be involved in speech intelligibility in noise [20] and in cochlea protection against noise [21], hyperacusis subjects could then be distinguished according to their difficulty to understand speech in noise, and their susceptibility to noise damage. In a group of hyperacusis patients including these criteria, MOC system could be more susceptible to be altered than in a group without those manifestations, or than controls. This study could then be improved increasing the two samples size and characterizing more accurately hyperacusis of each patient. An hyperacusis scale [22] recently created and including three dimensions (attentional, social, emotional) could help clarifying the various semiological aspects of hyperacusis.

The active cochlear mechanisms also explored in this study through TEOAE amplitude recording did not prove to be different in the two samples. It does not seem that outer hair cells functioning is altered in hyperacusis. The lateralization of TEOAE was found in both groups of subjects and confirmed previous results [23].

At the auditory periphery, outer hair cells seem to function normally in hyperacusis patients, whereas the MOC system could be less efficient in some hyperacusis subjects, especially in their right ear.

Subjective measurements of hyperacusis

Goldstein and Shulman [6] found that hyperacusis could be identified by loudness discomfort level test and ADR. However, in the present study, even if tendency for lower ADR in hyperacusis patients than in controls was noticed in figure 3 supporting previous results [6], the intergroup difference was not statistically significant. It could be that this ADR measurement is not sensitive enough to clearly distinguish between hyperacusis and nonhyperacusis subjects, although it contribute to hyperacusis assessment.

On the contrary, the LGOB test allowed to statistically differentiate the two samples. This loudness growth estimation seems to be a test more appropriate than ADR to measure hyperacusis all the more since it gives a more precise information. The two psychoacoustical tests employed here could be complementary to quantify and characterize hyperacusis.

These psychoacoustical measurements, the MOC system functioning recording and the use of a validated questionnaire of hyperacusis could be included in a standardized methodology for hyperacusis assessment under various aspects.

As in some patients with tinnitus, MOC system could be less functional in some hyperacusis subjects. To confirm the hypothesis that hyperacusis could constitute a pretinnitus state [10] a longitudinal study should be used, to follow evolution of hyperacusis and symptoms associated. It could also be of interest to test the hyperacusis of patients with

tinnitus using the LGOB test which has appeared to constitute a sensitive marker of hyperacusis.

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Effects of intense sound on spontaneous activity in the dorsal cochlear nucleus and its relation to tinnitus

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Increased spontaneous activity (hyperactivity) has been implicated as an underlying neural correlate of tinnitus. Evidence is presented to show that exposure to an intense tone (10 kHz, 125–130 dB SPL) induces hyperactivity in the dorsal cochlear nucleus (DCN) of hamsters. This hyperactivity develops during the first week after exposure increasing slightly over a period of several weeks. The spread of hyperactivity across the DCN is initially broad, but becomes more and more sharply focused on a specific frequency band of the DCN over the first month after exposure. Our behavioral studies indicate that the same sound exposure that induces hyperactivity in the DCN also induces tinnitus in hamsters. Additionally, recordings from the DCN of animals previously tested for tinnitus indicate a strong correlation between the behavioral measures of tinnitus and the level of spontaneous activity ($r = 0.91$). Animals that tested positive for tinnitus also showed high levels of spontaneous activity, while those which tested negative showed low levels of spontaneous activity. These results suggest that there is a strong relationship between the level of spontaneous activity in the DCN and the severity of tinnitus resulting from acoustic overexposure. We discuss some of the possible neuronal and neurochemical mechanisms leading to this hyperactivity and possible means by which the hyperactivity, and presumable tinnitus, might be reversed.

Introduction

It has been hypothesized that tinnitus results from increases in spontaneous neural activity (hyperactivity) in the auditory system. Evidence in support of this hypothesis has been obtained from electrophysiological, metabolic, and behavioral studies in animals using salicylates and quinine. Animals exposed to moderate doses of salicylate or quinine, common causes of acute tinnitus, develop tinnitus-like percepts [1–3] as well as increased spontaneous activity at various levels of the auditory pathway [4–13]. Behavioral studies suggest that the tinnitus induced in animals by salicylate parallels the pattern of salicylate-induced tinnitus in humans both in its time course and psychophysical attributes [1–2].

Increases in spontaneous activity have also been shown to occur as a consequence of exposure to intense sound, a major cause of chronic tinnitus. When hamsters or rats were exposed to a high frequency tone at a level of 127 dB for 4 hours, spon-

aneous activity in the dorsal cochlear nucleus increased several fold above normal levels [14–16]. However, the relationship of this hyperactivity to tinnitus has been unclear because there is no evidence that the same exposure causes tinnitus in hamsters.

To fill this gap, our research group has recently used behavioral techniques to determine whether hamsters exposed to intense sound develop tinnitus-like percepts, and if so, whether the same animals with tinnitus also show evidence of hyperactivity in the dorsal cochlear nucleus. To address these issues, animals were first tested behaviorally for tinnitus using a conditioned avoidance paradigm. After completion of the behavioral tests, the same animals were then studied electrophysiologically by recording spontaneous activity in the DCN. This dual experimental approach in the same animals enabled us to determine whether the behavioral evidence for tinnitus is correlated with the magnitude of hyperactivity in the DCN.

Methods

To test for tinnitus, 10 hamsters were trained using a conditioned avoidance procedure to drink from a

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water spout whenever a noise or tone was present, but to cease drinking during silent periods. This was done by presenting 15-s intervals consisting randomly of either "safe" trials in which a noise or tone was presented, or "warning" trials in which no external sound was presented and which were followed by a shock delivered through the water spout. The animals soon learned to maintain contact whenever a noise or tone was present and to avoid the shock by breaking contact with the spout during the silent trials.

The response of an animal was measured by recording the amount of time it was in contact with the water spout during the last half (7.5 s) of each trial. Overall performance was determined by comparing the percent time it broke contact during silent trials ("hit rate") with the percent time it broke contact during noise or tone trials ("false alarm rate"). The hit rate was corrected for false alarms using the formula: Performance = Hit rate - (False alarm rate × Hit rate). The animals soon became reliable observers and correctly detected the presence or absence of a 10 kHz tone or broadband noise. Additional training was given using frequencies from 8 to 22 kHz in 2 kHz steps to ensure that the hamsters would generalize to other tones.

Although tinnitus may be perceived as a loud sound of up to 70 dB sensation level (SL), the average loudness of tinnitus is perceived to be about 22 dB SL [17]. Because animals do not usually respond to such low level sounds without special training, the hamsters were also presented tones that were within 20 dB of their absolute threshold. Thus, the animals were experienced in reporting the presence of low level tones of various frequencies.

To induce tinnitus, 5 of the animals were anesthetized and their left ears exposed to a 10-kHz tone at an intensity of 125 dB SPL for 4 hours, the same tone which was previously shown to induce hyperactivity in the DCN [14-16]. All of the hamsters were housed in a room with a continuous masking noise to reduce the possibility that they would hear, and thus habituate to, any tinnitus they might develop.

Within 2-10 days after being tested behaviorally for tinnitus each of the 10 animals was subsequently studied electrophysiologically. The DCN was surgically exposed, and spontaneous activity was recorded at the surface of the DCN using micropipette electrodes. Only one electrode was used per animal, and recordings were performed in each of 3 rows of 13-15 sites (39-45 total sites) that spanned the mediolateral dimension of the DCN (Figure 2A). These recordings were performed without prior knowledge of the results of the behavioral experiments. At the end of the 10 experiments, recordings were averaged across rows within each animal, yielding a mean spontaneous rate for each of the 13-15 mediolateral loci. The results were plotted for each animal as spontaneous rate *vs.* distance along the DCN surface.

Results

The animals were tested for tinnitus beginning on the fifth day after sound exposure [18]. The test consisted of the same basic task with two differences. First, the silent trials were no longer followed by shock, making it an "extinction" test. Second, only the noise stimulus was presented on sound trials. This was done in the belief that the tinnitus would likely be tonal and that the absence of an external tone would facilitate generalization to tinnitus as the animals had been trained to expect a tone. The animals were tested for 6 days during which they received an average of 22 silent trials per session. The scores on the silent and noise trials were compared to determine whether an animal was responding at a level above chance (Mann-Whitney U test).

Although all animals were expected to cease responding to the silent trials as a result of discontinuing the shock, it was predicted that the exposed animals would cease at a faster rate than the control animals as any tinnitus they developed might act as a signal that there was no impending shock and it was safe to drink. That the two groups differed as predicted is illustrated in two ways:

- (1) The avoidance responses of the exposed animals were significantly lower than those of the control animals (Figure 1A). This finding was statistically reliable for both the absolute scores for each animal and for the change in performance from the preceding training sessions ($p = 0.0033$, Mann-Whitney U). Indeed, the effect was strong enough to be detectable on the first and second days of testing alone ($p = 0.016$, Mann-Whitney U).
- (2) The exposed and control groups varied in the rate at which their performances fell to chance (Figure 1B). While all of the exposed animals had ceased responding to the silent trials by day 4, several of the control animals were still responding above chance on the last test session. The difference in the number of animals falling to chance was statistically reliable ($p < 0.01$, Chi-square).

Complete recordings were obtained from 9 out of the 10 animals tested behaviorally (one of the animals died after only one row of recordings). Of these 9 animals, one was excluded from the data analysis because of instabilities resulting from the presence of a large blood vessel traversing the DCN surface. The relationship between spontaneous rates and tinnitus was examined in three ways. First, spontaneous rates in exposed animals were compared with those in unexposed normal animals. This comparison was made by plotting the mean rate *vs.* distance relative to the 5 kHz isofrequency contour line of the DCN. Second, a linear regression analysis was performed to test the degree of correlation between the behavioral performance score and the maximal and total spontaneous rates recorded from the DCN. Third, the mean spontaneous rates obtained from the three animals with the lowest behavioral scores (*i.e.* those showing

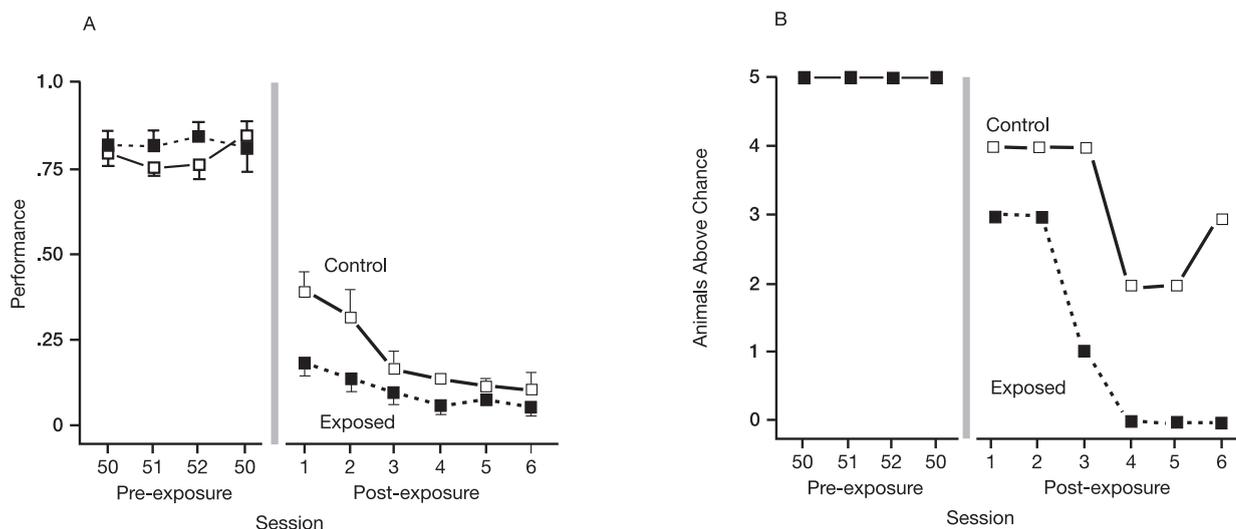


Figure 1 A. Average scores for 5 exposed (closed squares) and 5 normal (open squares) animals during the last four training sessions and the six test sessions shown with standard error bars. The consistently lower scores of the exposed animals are a sign of tinnitus, and the difference between the two groups is statistically reliable ($p = 0.0033$, Mann-Whitney U test). B. Number of exposed and normal animals responding at a level above chance ($p > 0.05$). Again, the more rapid extinction of the exposed animal is a sign of tinnitus, and the difference between the two groups is statistically reliable ($p < 0.01$, Chi-square test).

the strongest evidence of tinnitus) were compared with those obtained from the three animals with the highest behavioral scores. This approach was more meaningful than comparing means of all exposed animals with those of controls for two reasons: (a) not all exposed animals showed equally strong evidence of tinnitus, and (b) animals between the extremes (those with the highest and lowest behavioral scores) were less clearly differentiated both in terms of behavioral performance and spontaneous rates.

A comparison of spontaneous rates in exposed and unexposed animals is presented in the two graphs of Figure 2B. This comparison reveals a conspicuous difference in spontaneous rates between the two groups, especially in the middle portion of the DCN spanning the range between 0.2 and 0.8 mm from the 5 kHz contour line. In this range, all four exposed animals (left panel) showed rates which were higher than 75 events/second, with maximum rate averaging 85 events/sec. In contrast, all four unexposed animals (right panel) showed rates that were consistently lower than 50 events/second in the same topographic region of the DCN, with maximum rate averaging 28 events/sec. Spontaneous rates in two of the unexposed animals did not exceed 10 events/second at any position along the DCN.

The results of the linear regression analysis are shown in Figure 3A. The data show that there was a progressive decrease in behavioral performance with increase in maximal spontaneous rate. The coefficient of correlation, r , between behavioral score and maximal rate was equal to 0.91 ($p = 0.002$). This correlation was not limited to maximal spontaneous rate; a strong correlation was also found between the behavioral performance scores

and the spontaneous rate computed by summing rates across all recording sites in each animal ($r = 0.77$, $p = 0.026$).

Just how tinnitus may be revealed in the spontaneous rates is best shown by comparing the mean rate of the 3 animals with the strongest evidence of tinnitus (lowest behavioral scores) with the mean rate for the 3 animals with the least indication of tinnitus (highest behavioral scores). As can be seen in Figure 3B, animals differing strongly in behavioral performance scores were also very well differentiated in terms of spontaneous activity. Not only were spontaneous rates generally higher overall across most of the DCN in the hamsters that were strongly positive for tinnitus, but the greatest differences in activity were observed in the middle of the DCN (see arrow under abscissa) just medial to the region which normally represents the frequency of the exposure tone. Thus, at the 0.7-mm locus spontaneous rates in exposed animals averaged 75 events/sec while those at the corresponding position in unexposed animals averaged 15 events/sec ($p < 0.02$).

Discussion and conclusion

These observations suggest that the behavioral evidence for tinnitus following intense sound exposure is linked with the level of spontaneous activity in the DCN. Animals showing the strongest behavioral evidence of tinnitus showed the highest rates of spontaneous activity, and conversely, those with the lowest indications of tinnitus showed the lowest spontaneous activity.

At what neural level does the hyperactivity induced by intense sound exposure originate?

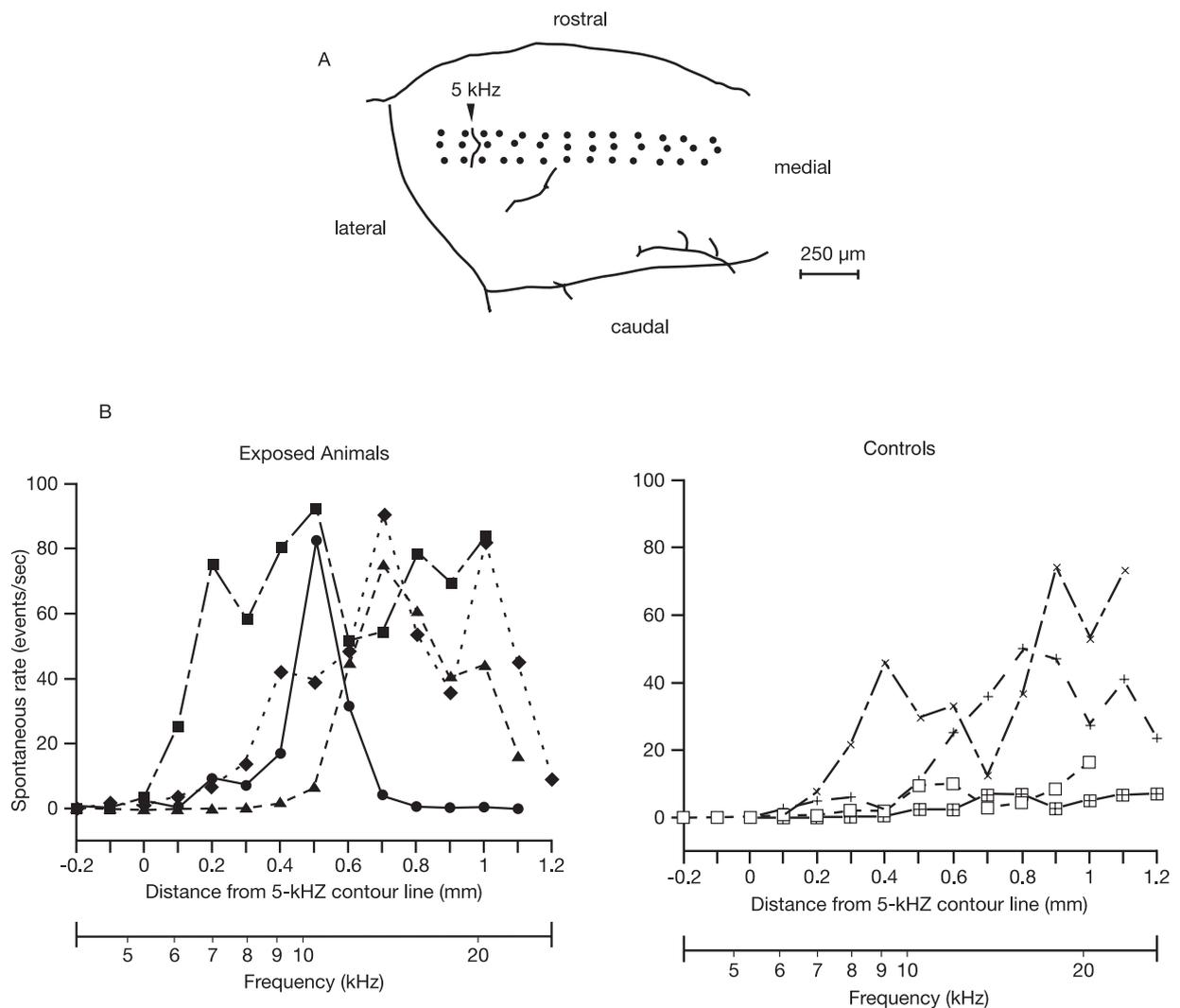


Figure 2 A. Dorsal view of the left DCN (bold outline) of a hamster showing the distribution of sites (dots) where recordings of spontaneous activity were performed. The sites are laid out in three rows that run parallel to the mediolateral axis of the DCN. Recording sites in each animal were localized topographically by measuring their distance (in mm) from the 5 kHz isofrequency contour (arrowhead). The 5 kHz contour line was determined at the end of each mapping session by testing the spectral responses of neural clusters in the lateral third of the DCN. B. Spontaneous rates *vs.* distance along the DCN surface for 4 tone-exposed hamsters (left panel) and 4 unexposed control hamsters (right panel). The frequency axis based on previous studies of the DCN is included below the abscissa. All hamsters had previously been tested behaviorally for tinnitus. The recordings and analysis of spontaneous activity were performed without knowledge of the results of the behavioral tests. Note that between 0.2 and 0.8 mm all of the exposed hamsters displayed maximal rates of 75 or more events/sec, whereas in the corresponding locations, the control animals displayed maximal rates of 50 or less events/sec with two of the animals displaying counts of less than 20 across the entire DCN. Symbols indicate individual hamsters.

Although the present study did not address this issue directly, insight can be gleaned from previous studies that found spontaneous activity of auditory nerve fibers to decrease following recovery from intense noise exposure [19]. Subsequent studies showed that the magnitude of the decrease was proportional to the amount of damage to cochlear inner hair cells [20]. In view of these considerations, it seems likely that the changes in spontaneous activity observed in the DCN after intense sound exposure do not originate peripherally, but instead, represent a secondary consequence of altered peripheral input.

What mechanism underlies the induction of hyperactivity? One possibility is that intense sound

causes damage to the cochlea which, in turn, triggers an imbalance between excitatory and inhibitory inputs to the DCN. This change in balance could result in a disinhibition of DCN neurons leading to increased spontaneous activity. Such a mechanism is consistent with previous evidence showing that overexposure to noise can cause chronic alterations in single unit auditory response patterns as well as hyper-responsiveness of central auditory neurons to sound [21–22]. A second possibility is that loss of normal input to the DCN from the auditory nerve might trigger a compensatory increase in efferent gain as part of a central response to reduced peripheral input. This increase in gain might feed back to DCN neurons boosting

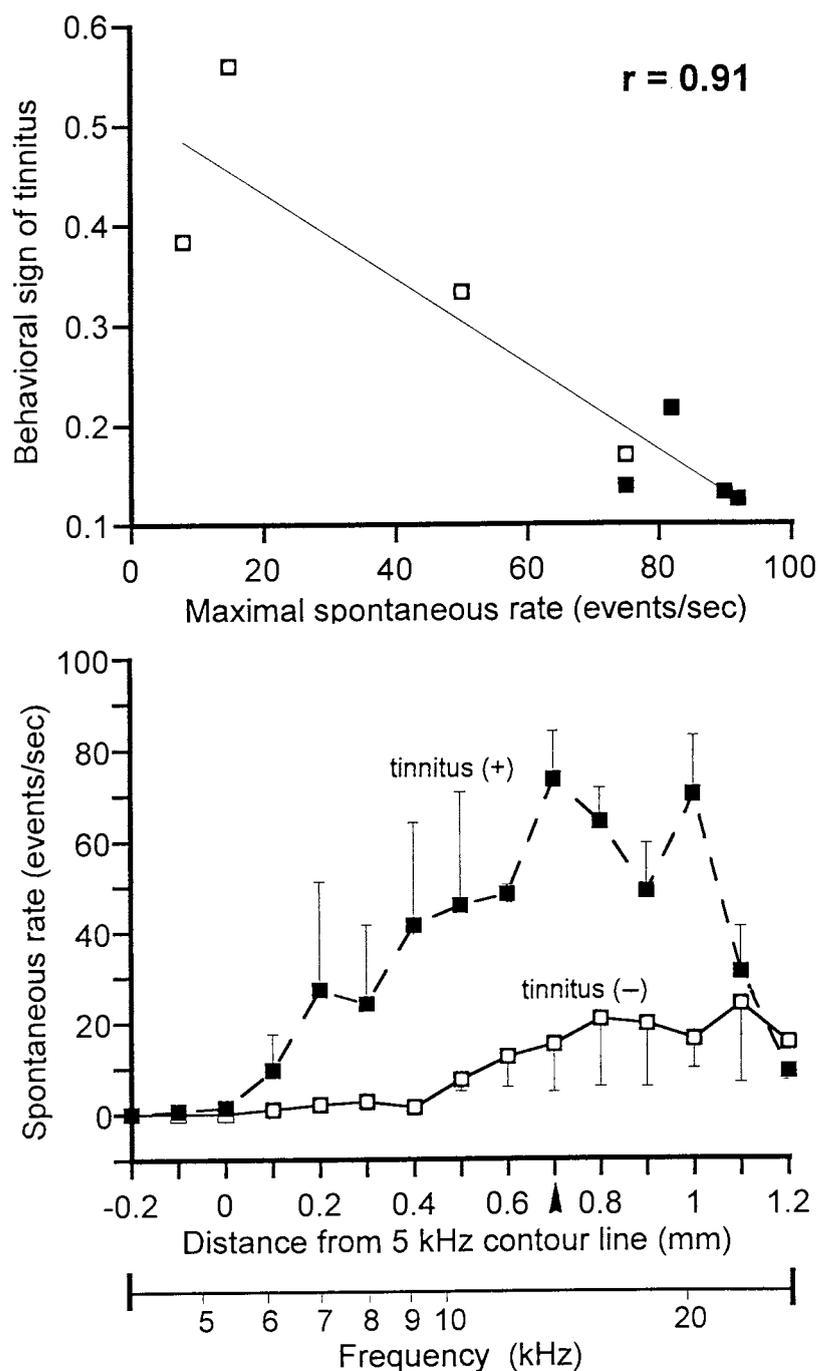


Figure 3 Maximal spontaneous rate in the DCN is related to the degree of tinnitus. A. Behavioral sign of tinnitus is plotted as the reciprocal of each animal's behavioral score. Maximum rate is the highest multiunit spontaneous rate irrespective of tonotopic location. Each point represents a single animal. Control animals are represented by open squares, tone exposed animals by solid squares. B. Comparison of mean spontaneous rates \pm SEM. *vs.* distance for the 3 animals having strongest evidence of tinnitus (solid squares) and the 3 animals having the least indication of tinnitus (open squares). The frequency axis based on previous studies of the DCN is included below the abscissa. Arrow indicates the frequency locus showing the greatest group difference.

their resting level of activity. Studies that define the locus and morphological characteristics of hyperactive cells would be of value for an understanding of the neural mechanisms of noise-induced tinnitus.

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The effects of lidocaine on salicylate-induced spontaneous firings in the auditory midbrain

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In order to examine the possibility that the local anesthetic lidocaine acts on the inferior colliculus (IC) to temporarily relieve tinnitus, effects of lidocaine on firings of IC neurons were monitored in an animal tinnitus model using extracellular recording techniques. The tinnitus model was created by the intravenous injection of sodium salicylate (200 mg/kg) into adult guinea pigs. The discharge of IC neurons was suppressed by intravenously administered lidocaine at a concentration used clinically (1 mg/kg). It was revealed that IC neurons could be classified into two groups according to the difference in the sensitivity to lidocaine: (1) weakly-sensitive neurons (15/22) and (2) highly-sensitive neurons (7/22). The duration of the lidocaine action was less than five min in weakly-sensitive neurons, whereas it lasted for longer than 30 min in highly-sensitive neurons. Use-dependent block of firings by lidocaine is suggested because the inhibitory action of lidocaine was enhanced as the firing rate of IC neurons was increased. The latency to sound stimulus (a clicking sound 80–90 dB) was between 5–15 ms in highly-sensitive neurons, and it was more widely distributed (5–45 ms) in weakly-sensitive neurons. For weakly-sensitive neurons the discharge was more strongly suppressed by lidocaine when the latency to sound stimulus was prolonged. It is to be noted that the long inhibitory action of lidocaine can only be achieved in the presence of salicylate, since only weakly-sensitive IC neurons were detected in guinea pigs which had not been injected with salicylate.

Introduction

Temporary relief from tinnitus can be obtained in some patients by the intravenous injection of the local anesthetic lidocaine [1]. Tinnitus has been ascribed to the perception of abnormal spontaneous activity in the auditory system [2], and lidocaine is considered to suppress such neuronal firings in the auditory pathways [3,4]. Although the exact active site in the auditory system for lidocaine and the mechanism of the drug action on the neuronal discharge are not yet fully understood, Ruth *et al.* [5] reported that the waves reflecting the activity of IC neurons were suppressed by lidocaine at 1 mg/ml. Thus, we have decided to work on an animal tinnitus model, created by sodium salicylate, to investigate the effects of lidocaine on the discharge of IC neurons.

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Methods

Guinea pigs (400–450g) which showed positive Preyer pinna reflexes were used for experiments. A guinea pig was anesthetized with urethane (1.5 g/kg), tracheotomized for artificial respiration, and was fixed to a conventional stereotaxic frame with hollow ear bars through which sound stimulus was applied (Figure 1). The inferior colliculus (IC) was exposed by making a hole (approximately 10 mm in diameter) in the skull followed by removal of the overlying cerebral cortex by aspiration. Firings of IC neurons were recorded with glass microelectrodes filled with 2M NaCl (15–25 M \bullet) using the conventional extracellular recording method. Sound stimulus (clicking sound; 80–90 dB, 5 Hz), generated by an audible signal controller (DA-502AM; DANA, Tokyo), was applied to the ear of the animal in a soundproof room [6]. Neuronal discharge rates (spikes/s) were measured and post-stimulus time histograms (PSTH) with a bin-width of 0.5 ms were created using a computer. Both salicylate (Wako, Japan) and lidocaine hydrochloride were administered intravenously to guinea pigs

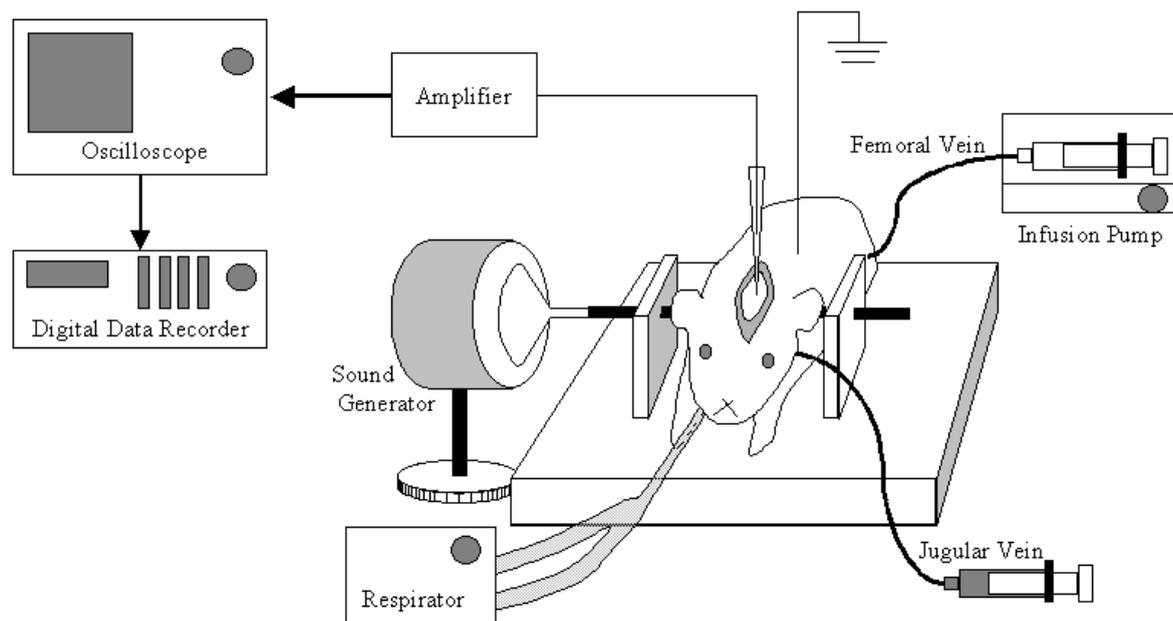


Figure 1 Schematic diagram of the experimental set-up for the present work. See Methods for details

through the femoral vein using an infusion pump (JP-S-E; Furue, Tokyo).

Results

An animal tinnitus model was created by administering 5 ml of physiological saline solution (0.9% NaCl) containing sodium salicylate (200 mg/kg) over 15 min. As shown in Figure 2, the spontaneous

discharge of IC neurons was significantly augmented by salicylate (open circles). In animals injected with only physiological saline, the firing rate was 5.62 ± 0.41 Hz ($n = 13$), and the value was not significantly different from the rate 4.84 ± 0.71 Hz ($n = 74$) obtained in non-injected guinea pigs. Closed circles indicate the serum concentration of salicylate measured by the Jolley method [7] using blood taken from the jugular vein. The measured salicylate concentration was approximately 45 mg/

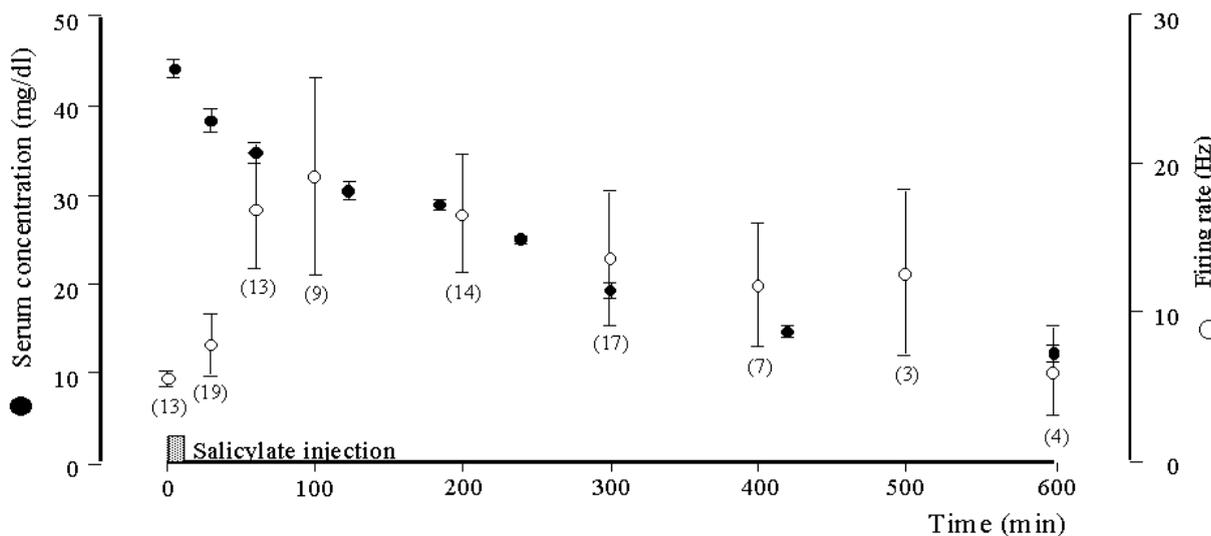


Figure 2 The effect of salicylate on the spontaneous discharge of inferior colliculus (IC) neurons of the guinea pig. Salicylate was administered to animals over 15 min starting at time zero (shaded bar). Open circles: firing rate of IC neurons (mean \pm SE; the number of neurons in brackets). Filled circles: time course of the serum concentration of salicylate ($n = 8$) measured at the jugular vein. The abscissa indicates the time relative to the starting point of the salicylate injection. The ordinate shown to the left of the plots is for the serum concentration of salicylate in mg/dl and that displayed to the right is for the firing rate of neurons in Hz. (Reprinted from Manabe *et al.* 1997 [6] with permission from Elsevier Science.)

dl immediately after salicylate injection and it exponentially declined to less than 15 mg/dl around 500 min after. The graph shows that the neuronal discharge was increased by salicylate in a dose-dependent manner. When the concentration of serum salicylate dropped to less than 15 mg/dl, firing rate of IC neurons declined to the level before salicylate injection. Since salicylate concentration above 15 mg/dl has been reported to evoke hearing loss with an accompanying tinnitus in humans [2,8], it seems reasonable to conclude that this animal tinnitus model is suitable for studying the effect of lidocaine on tinnitus.

The effect of lidocaine on salicylate-induced discharge of IC neurons was examined. Stable unitary recordings for longer than 30 min could be obtained from 30 neurons: 22 neurons after salicylate injection and 8 neurons before salicylate injection. Three patterns of discharge inhibition were observed as illustrated in Figure 3: (A) complete inhibition of the neuronal discharge over 30 min (in 7/22 neurons after salicylate injection, and in 0/8 neurons before injection), (B) brief disappearance of the discharge for less than five min (in 3/22 neurons after and 2/8 before injection), and (C) incomplete inhibition of the discharge (in 12/22 neurons after and 6/8 before injection).

During experiments, we noticed that the inhibitory action of lidocaine (Figure 3) was somehow correlated with the latency to sound stimulus. In order to verify this idea, we measured the latency to the onset of the spike. The latency varied from neuron to neuron as shown in Figure 4. Representative examples are displayed in the post-stimulus time histograms with a bin width of 0.5 ms. Note

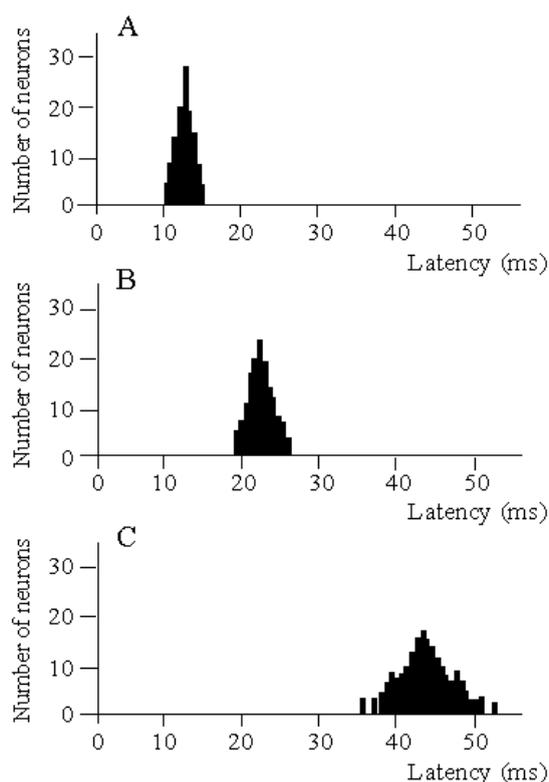


Figure 4 Histograms showing the latency of representative IC neurons in response to clicking sound stimulus. (A): An IC neuron with a short latency and a narrow distribution, 12.2 ± 1.0 ms ($n = 126$; number of stimulus trials). (B): A neuron with medium latency and distribution, 23.9 ± 1.5 ms ($n = 126$). (C): A neuron with a long latency and a wide distribution, 43.4 ± 3.9 ms ($n = 126$). The bin width is 0.5 ms. (Reprinted from Manabe *et al.* 1997 [6] with permission from Elsevier Science.)

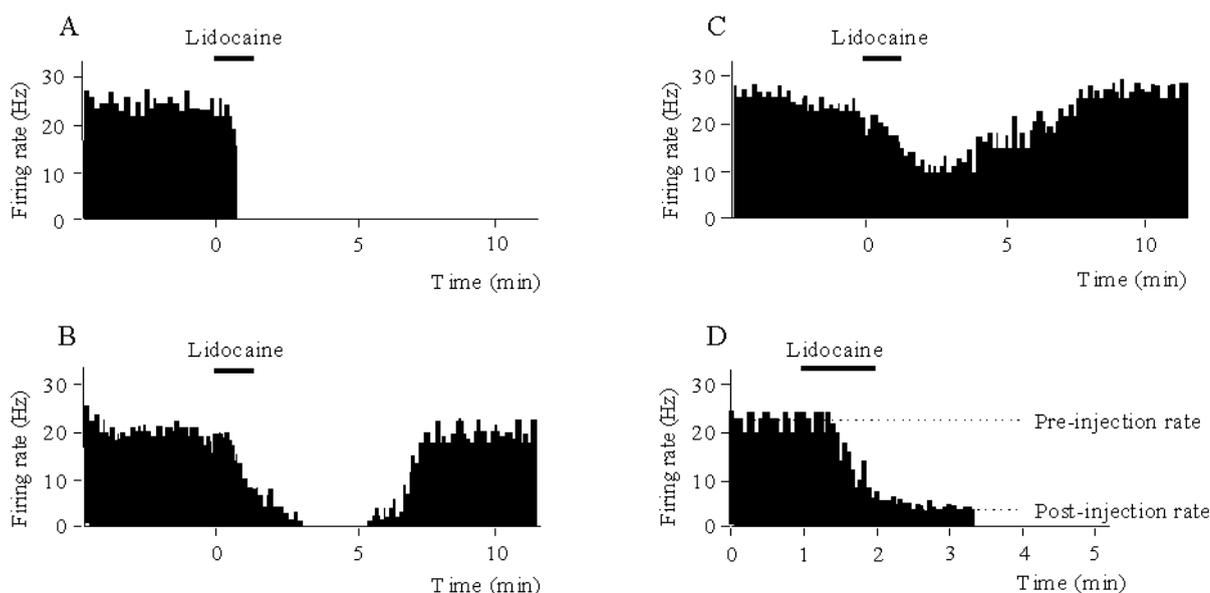


Figure 3 The inhibitory effect of lidocaine on the discharge of IC neurons. The intravenous application of lidocaine (1 mg/kg) is indicated by the horizontal bars. Three patterns of lidocaine inhibition (A-C) are illustrated. A: Complete inhibition of the neuronal discharge over 30 min. B: Complete suppression of the discharge for less than five minutes. C: Partial inhibition of the discharge. D: A schematic graph showing the effect of lidocaine on the discharge of an IC neuron. Pre- and post-injection rates indicate the average firing rate of the neuron before and after injection of lidocaine. (Reprinted from Manabe *et al.* 1997 [6] with permission from Elsevier Science.)

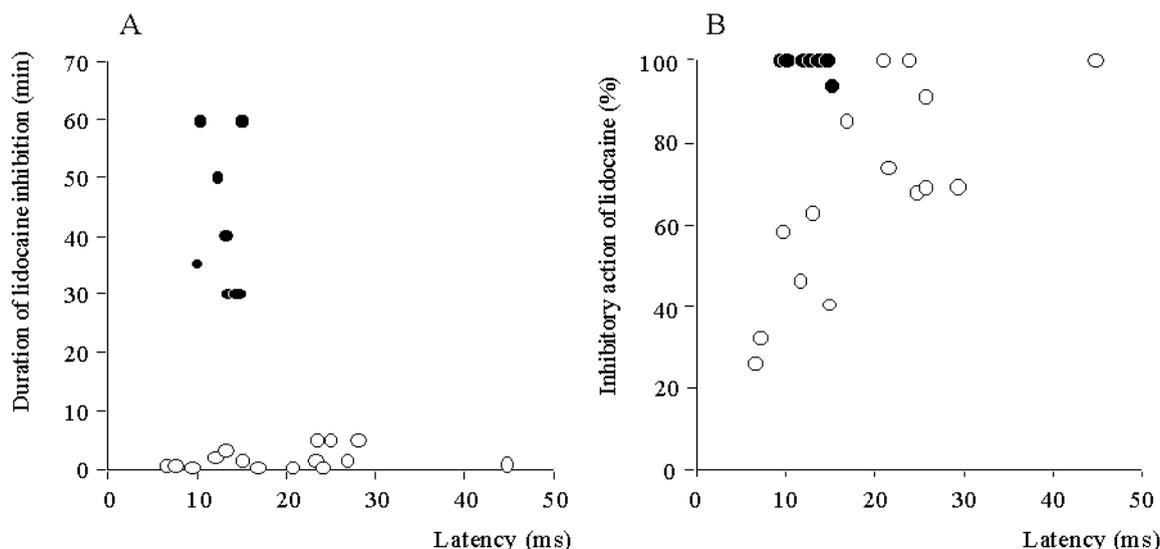


Figure 5 Classification of IC neurons into two groups. A: Relationship between the duration of lidocaine inhibition and the latency to the sound stimulus. Neurons shown as open and filled circles are named as weakly- and highly-sensitive neurons because they exhibited short and long duration of the lidocaine effect, respectively. B: Relationship between the inhibitory action of lidocaine and the latency to the sound stimulus. Open and filled circles indicate the same groups of neurons shown in A. (Reprinted from Manabe *et al.* 1997 [6] with permission from Elsevier Science.)

that the distribution of the latency values was wider as the latency became longer.

Figure 5A, plotting the duration of lidocaine inhibition against the sound latency, clearly shows that our idea seems to be right. The plots reveal two distinct groups of IC neurons. A group of neurons, indicated by filled circles, were highly sensitive to lidocaine and their discharge was completely or almost completely inhibited by lidocaine for longer than 30 min. Another feature of these neurons is the short latency with small distribution. We call this group of neurons as “highly-sensitive” neurons hereafter. In the other group of neurons (open circles), the duration of lidocaine inhibition was considerably shorter (less than five minutes) when compared with that of highly-sensitive neurons. The latency to sound stimulus varied from neuron to neuron. These neurons, therefore, will be called “weakly-sensitive” neurons.

The inhibitory action of lidocaine on the discharge of IC neurons was further estimated by introducing the parameter “inhibitory action of lidocaine” which is defined by the following equation (see Figure 3D):

$$\text{Inhibitory action of lidocaine (\%)} = \frac{(X - Y)}{X} \times 100$$

where X = the firing rate measured before the injection of lidocaine (pre-injection rate), and Y = the steady-state firing rate measured in the presence of lidocaine (post-injection rate)

Figure 5B displays the relationship between the inhibitory action of lidocaine and the latency to sound stimulus. Plots were obtained from the same neurons shown in Figure 5A. The discharge of highly-sensitive neurons (also indicated by filled circles) was completely inhibited in most cases, and the parameter (inhibitory action of lidocaine) was 100 or close to 100%. In contrast, the parameter

was correlated with the latency to sound stimulus in weakly-sensitive neurons. A complete inhibition of the discharge was observed in a small number of neurons, and the neuronal discharge was more strongly suppressed by lidocaine when the latency to sound stimulus became longer.

The relationships displayed in Figures 5A-B can be simultaneously shown in a three-dimensional graph (Figure 6). It clearly differentiates a group of highly-sensitive IC neurons (bars with filled heads) from other neurons, because of their strong and long lidocaine inhibition. The graph also shows that such neurons have short latency (around 10 ms) to sound stimulus. Another group of neurons, weakly-sensitive neurons (bars with open heads), are more widely scattered and have a shorter duration of lidocaine inhibition. Interestingly, control neurons (bars with shaded heads), which were not exposed to salicylate, have similar properties to those of weakly-sensitive neurons, especially the duration of lidocaine inhibition was less than five min. It is suggested that salicylate prolongs the duration of lidocaine action in some IC neurons.

During the course of experiments, we have noticed that IC neurons firing at high frequencies were more rapidly inhibited by lidocaine than those firing at low frequencies. In order to test this idea, the decay phase of the firing-rate histogram (see Figure 3) was calculated. It was found that the decay phase could be fitted by a single exponential curve, i.e. the decay of the firing rate was a first-order process. The time constant of an exponential curve was calculated, and the value ranged from 0.087 to 27.6 s. Figure 7A prominently shows that the time constant of the inhibition curve of the discharge became smaller with increasing firing rate, i.e. the firing of IC neurons declined faster as the discharge rate of neurons was increased. In add-

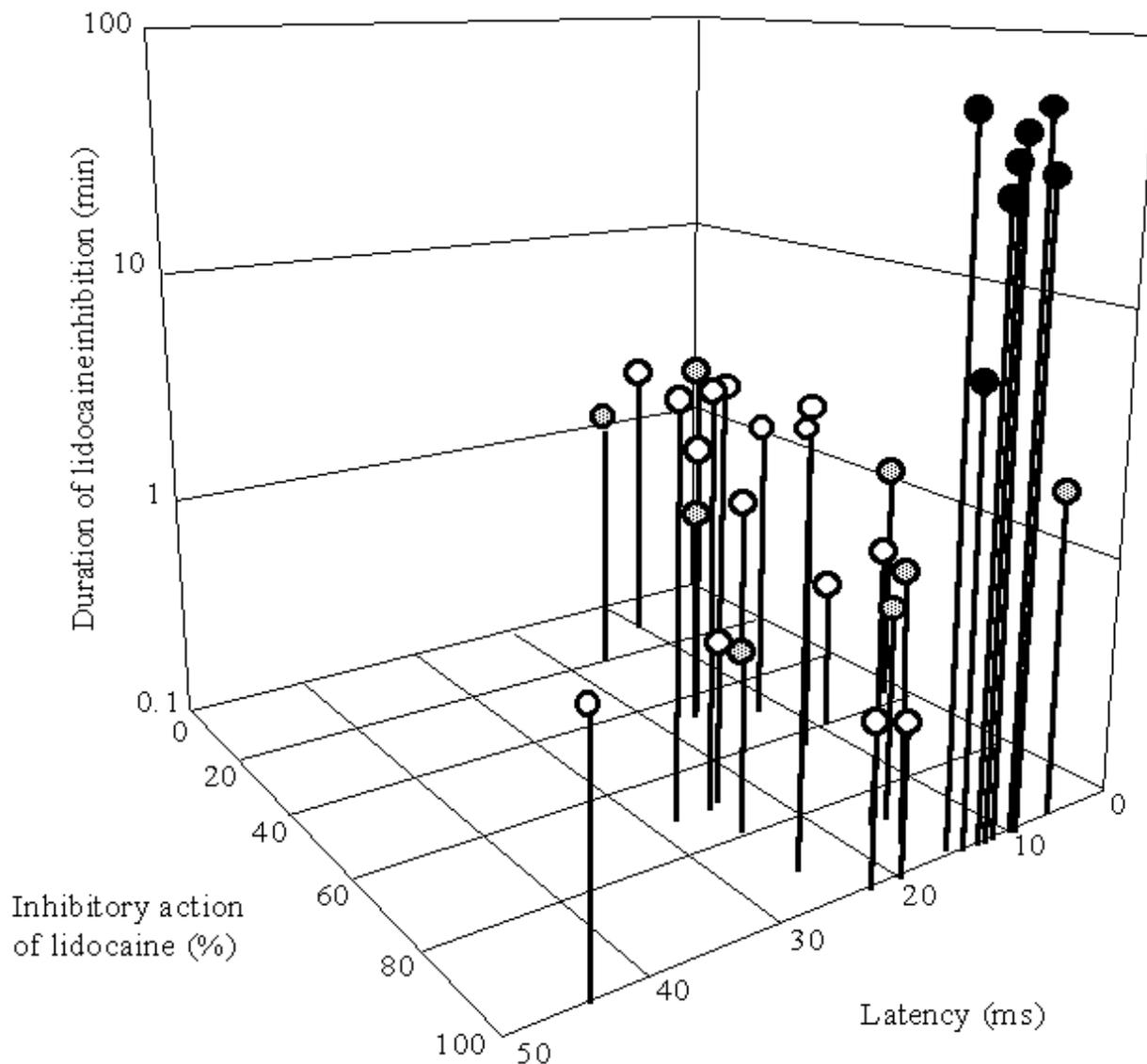


Figure 6 Three-dimensional graph showing the relationships between (1) inhibitory action of lidocaine, (2) the latency to sound stimulus, and (3) duration of lidocaine inhibition. Highly-sensitive neurons are indicated by bars with filled heads, weakly-sensitive neurons by bars with open heads, and control neurons by bars with shaded-heads. Control neurons were not exposed to salicylate.

ition, it was found that the latency of the lidocaine action was shorter when IC neurons were firing at high frequencies. The latency of the lidocaine action indicates the time measured from the point of lidocaine application to the point where the firing rate started to decline. These results show that the inhibitory action of lidocaine appears faster and acts more rapidly in IC neurons firing at higher frequencies.

Discussion and conclusion

The injection of local anesthetics (lidocaine, procaine) is known to temporarily relieve tinnitus in humans [1,9–11]. The mechanisms of the lidocaine action on the auditory system have been studied in animals such as the guinea pig [12–14] and the cat [3,4]. However, the lidocaine concentration they

used was much higher than the concentration used clinically (1 mg/kg). The present study has shown, for the first time, that the discharge of IC neurons is reversibly inhibited by intravenous injection of lidocaine at 1 mg/kg (Figure 4). This reversible inhibition of the neuronal activity would account for the reported relief from tinnitus in humans by lidocaine.

The mechanisms of tinnitus have been studied using an animal tinnitus model created by sodium salicylate [15,6]. Evans *et al.* [17] observed that salicylate induced spontaneous discharge in a single cochlear nerve fiber of the cat, but the discharge was little affected by an intravenous application of lidocaine at a clinical dose (1.5 mg/kg) for humans. It was confirmed by Schreiner *et al.* [3] and Martin *et al.* [4] that the spontaneous cochlear nerve activity evoked by salicylate was temporarily suppressed by an injection of lidocaine. However, their dose of

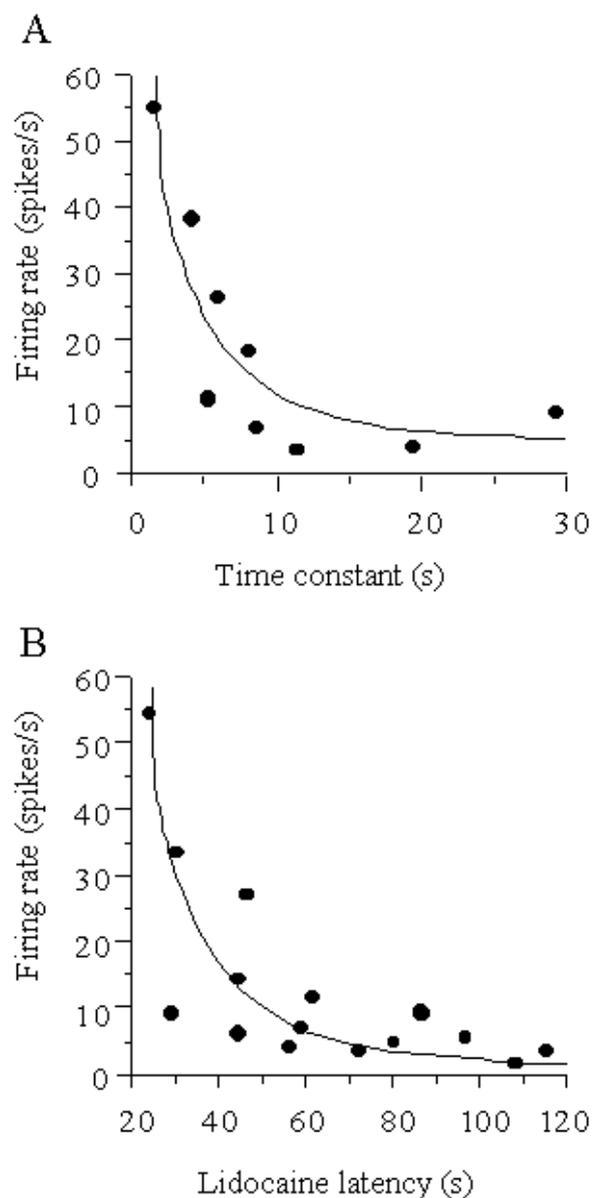


Figure 7 Firing rate of IC neurons plotted against the time constant of the decay of the firing rate (A) and the latency of the lidocaine action (B). See text for further explanation.

lidocaine was 6 mg/kg; 4 times larger than that used by Evans and his co-workers. Ruth *et al.* [5] studied the influence of lidocaine (1 mg/kg) on the auditory brain-stem responses. Although waves I and III were unaffected by lidocaine, wave V (resulting from the activity of IC neurons) exhibited significant decrease in amplitude and increase in latency. They concluded that the more central component of the auditory system than cochlear nerve fibers seemed to be the prominent site of action of lidocaine.

Our results not only showed a prominent inhibitory action of lidocaine on the neuronal discharge but also indicated that IC neurons could be classified into two groups according to their sensitivity to lidocaine. Highly-sensitive and weakly-sensitive IC neurons. The exact reason why lidocaine sensitivity

varies from neuron to neuron is unknown. However, it might be explained by the size of IC neurons, since there is a report that lidocaine worked more rapidly on small neurons than on large neurons [18].

It is interesting to know that control neurons, which were not exposed to salicylate, showed similar properties to those of weakly-sensitive neurons (Figure 6). This suggests that long-lasting inhibition of IC neurons by lidocaine can be achieved only in the presence of salicylate. In fact, sodium salicylate is reported to enhance the action of the local anesthetic procaine [19], and the onset of anaesthetic action became more rapid and the duration of action was prolonged in crayfish giant nerve fibers and in rat vagal nerves [20]. Similar enhancement mechanisms seem to be working on IC neurons as revealed in the present work.

Use-dependent block is a characteristic feature of local anesthetics which selectively block Na^+ channels, i.e. the accumulation of inhibition occurs with repetitive stimuli [21]. In the frog node of Ranvier, for example, the anesthetic action of lidocaine was enhanced by repetitive excitation [22]. It is to be noted that this frequency-dependent block of Na^+ channels by lidocaine requires open Na^+ channels. Lidocaine molecules enter Na^+ channels when they are open and bind to local-anesthetic receptors inside the channels, resulting in the prevention of Na^+ ions from going through the channel pores from outside [21]. The present results suggest that use-dependent block by lidocaine may occur in guinea pig IC neurons, since the inhibitory action of lidocaine on IC neurons became stronger when neurons were firing at higher frequencies (Figure 7). Thus use-dependent block of Na^+ channels by lidocaine seems to be a mechanism contributing to the suppression of the spontaneous discharge of IC neurons.

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Auditory cortex reorganization after noise trauma: Relation to tinnitus?

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Cortical topographic map changes have been reported after profound drug-induced hearing loss in neonates and after mechanical induced lesions in the cochlea of adult animals. The present study demonstrates that exposure of 5-week old kittens to a loud 6 kHz tone, producing mild-to-moderate high-frequency hearing loss, induces a profound reorganization of the frequency map in the auditory cortex. Spontaneous activity in the reorganized part of the cortex was significantly increased. The strength of the cross correlation of the spontaneous activity of units recorded on different electrodes was the same in the normal and reorganized part. This suggests that a change in spontaneous activity rather than changes in neural synchronization may be the neural substrate of tinnitus following noise trauma.

Introduction

A perceived sound that cannot be attributed to an external source is generally called tinnitus. Tinnitus is most likely the result of a prolonged discontinuity in the spatial activity pattern across fibers in the auditory nerve. This can be caused by a functional loss of outer hair cells in those regions where inner hair cells are preserved and may result in a reduction of inhibition at more central levels. In turn, this may cause hypersensitivity and hyperactivity in more central parts of the auditory system. Persisting changes in the normal cochlear output pattern across characteristic frequency may result in a slow reorganization of the tonotopical organized cortical areas with increased numbers of neurons tuned to a limited range of frequencies at the edge of the cochlear lesion. These edge-frequency neurons are likely to exhibit enhanced synchrony in their firings and, by their sheer number, enhanced sensitivity to peripheral activity changes. What evidence is there to support these statements? For that purpose we will first review some proposed neural substrates for tinnitus and then present some experimental findings related to induced changes in cortical topographic maps.

Auditory system organization and tinnitus

Because tinnitus is a perceptual phenomenon [1], the path to understanding it has to start at the sys-

tems level. The auditory system is a *massively parallel system* although it is presently not clear what sound features are processed in each of the many possible paths. The most peripheral sign of parallel processing is in the multi-fold innervation of the inner-hair cells by a set of auditory nerve fibers with different sensitivities. The second level of parallelism is found at the cochlear nucleus where each auditory nerve fiber trifurcates to project tonotopically to each of the three cochlear nucleus divisions. The inferior colliculus is the nexus between the lower auditory system and the thalamocortical system and is also considered the branching point for the lemniscal and extra-lemniscal pathways to the cortex. The lemniscal pathway is defined as strictly auditory, narrowly tuned to frequency, starting in the ventral cochlear nucleus and projecting in strict topographic fashion to the primary auditory cortex and the anterior auditory field. The extralemniscal pathway is more broadly tuned, more diffusely organized and is considered more plastic and context dependent [2], and also receives input from the somatosensory system. In the cat, the two lemniscal sections of the medial geniculate body feed dominantly into primary auditory cortex and anterior auditory field respectively, whereas the extralemniscal sections project to layers III/IV of secondary auditory cortex areas and also diffusely to layer I of all cortical areas.

The auditory system is also a *reentrant system* characterized by multiple, loosely interconnected, regional feedback loops [3]. The auditory cortex projects back to the medial geniculate body with 10 times as many fibers than the number of afferents from the medial geniculate body to auditory cortex. The auditory cortex also connects with the inferior

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colliculus, but with exclusion of the central nucleus [4]. The central and external inferior colliculus subnuclei both project back to the dorsal cochlear nucleus. The dorsal cochlear nucleus in turn feeds back to the ventral cochlear nuclei. The olivocochlear bundle projects via medial olivocochlear neurons to both outer hair cells and through the lateral olivocochlear neurons to low spontaneously active auditory nerve fibers synapsing with the inner hair cells [3]. It seems that the strongest contiguous projections from cortex to the auditory periphery involve the nuclei of the extralemniscal pathway and the dorsal cochlear nucleus.

Thus, as recognized before [5,6], the whole brain must somehow be involved in the sensation of tinnitus, specifically through the closed loop type interaction between the periphery and the CNS. Permanent changes in cortical organization will alter the descending activity from the auditory cortex to the periphery [7], especially through the components of the extralemniscal pathway in the thalamus and midbrain to the dorsal cochlear nucleus. Møller *et al.* [8] suggested the potential involvement of the extra-lemniscal system because tactile stimuli can interfere with the sensation of tinnitus. The observation of gaze-induced tinnitus [9,10] and recent studies by Cacace *et al.* [11,12] reporting cutaneous evoked tinnitus support this view.

Neural substrates of tinnitus

The general belief, expressed in the literature, is that most tinnitus results from altered spontaneous activity in the auditory nerve. Opinions then diverge as to which changes in auditory nerve fiber activity are causing the effect. Changes can occur at the individual neuron level, such as changes in spontaneous firing rate or in the temporal properties of single-neuron spike trains. Changes in population activity are also proposed, specifically in the synchrony of firings of subsets of neurons or in the changed activity patterns across characteristic frequency. I will review the rate, temporal and synchronization aspects of neural firing as they relate to proposed models for tinnitus.

The most straightforward theory is that *tinnitus results from an increased firing rate* in auditory nerve fibers generating an overall enhancement of activity in the central nervous system. However, insults to the auditory system that are accompanied by tinnitus generally decrease spontaneous firing rates in animal auditory nerve fibers [13,14,15]. Thus, increased firing rates in the auditory nerve are not likely to be causal to tinnitus. Evidence is now abundant for enhanced spontaneous activity after noise trauma in the dorsal cochlear nucleus [16,17]. Chen and Jastreboff [18] and Manabe *et al.* [19] have demonstrated increased spontaneous activity in the external nucleus of the inferior colliculus which is the proposed branching off point of the extralemniscal pathway. If this is the case, then a more likely cortical area for the detection of changes in spontaneous activity is the secondary auditory cortex that receives a strong direct input from the

extralemniscal pathway. Recently, Eggermont and Kenmochi [20] demonstrated that increased spontaneous activity was indeed present in secondary auditory cortex, but not in primary auditory cortex and anterior auditory field, after salicylate and quinine application.

It is also conceivable that *tinnitus is caused by a pathological reorganization of spontaneous firing patterns* resembling that found during sound stimulation. Eggermont [21] suggested that changes in the temporal structure of spike trains are sufficient to produce auditory sensations. Burst firing in the central nervous system has commonly been attributed to activation of NMDA-type glutamate receptors. Pujol [22] reported the presence of NMDA as well as non-NMDA glutamate receptors on Type I afferent fibers (that innervate the inner hair cells) in the auditory nerve. Normally, these NMDA receptors are only affected by high intensity sound but abnormal activity of NMDA receptors may result in spontaneous epileptic-like spike bursts. This was proposed as a likely cause of tinnitus. Activation of NMDA receptors in the spinal cord also appears to be critical in the production of chronic pain [23] a condition often likened to tinnitus [24,25]. If spontaneous bursting manifests itself throughout the auditory system, it may be one of the substrates for tinnitus.

In most studies involving damage to the cochlea [13,14,26], an increase in the number of spike pairs and short bursts is observed in those fibers with reduced spontaneous activity. Increased burst firing also occurs after salicylate application in the external nucleus of the inferior colliculus [18]. Whereas cortical neurons tend to burst in synchrony with EEG-spindles [27], the amount of bursting observed in cortex after salicylate or quinine application does not change [28,29].

Eggermont [21] and Møller [30] pointed to *inter-neural synchronization* as a general phenomenon underlying any sound sensation, stimulus induced or pathological. Increased interneuronal synchrony has been established in the primary auditory cortex of the cat after application of both sodium salicylate and quinine hydrochloride [28,29]. It is not clear if this increased synchrony in cortex is the result of an upward propagated synchrony from the level of the auditory nerve [31] or if it reflects an additional central effect of these drugs.

The pitch of tinnitus resulting from noise trauma is frequently similar to the characteristic frequencies on the edge of the damaged area. Meikle [32] proposed that the combination of a cortical reorganization with hypersensitivity of neurons near the edge of the damaged area provides the substrate for tinnitus. Salvi *et al.* [17] suggest in their "tuned-cluster" model of tinnitus that "large clusters of cortical neurons tuned to a narrow frequency range could give rise to phantom auditory sensations, particularly if the neural activity in these clusters were to become synchronized, as often happens in cases of epilepsy. This type of population coding does not require an increase in discharge rate of individual neurons".

Hearing loss changes the tonotopic organization of the auditory system

Restricted high-frequency cochlear damage results in a profound reorganization of the auditory cortex [33,34,35]. The effect is that the area of contralateral auditory cortex in which the lesioned frequency range would normally be represented becomes partially occupied by an expanded representation of frequencies adjacent to the range damaged by the lesion, with normal thresholds for these frequencies. This reflects a gradual reorganization since the responses of neuron clusters examined within hours of making similar cochlear lesions showed only small shifts in characteristic frequency towards frequencies spared by the lesion, with greatly elevated thresholds compared to normal. In contrast, the map of the unlesioned ipsilateral cochlea does not differ from those in normal animals. Thus, in the lesioned animals ipsilateral and contralateral tonotopic maps in the same cortical hemisphere differ in the region of the lesion only, in contrast to the normal very good matching of ipsilateral and contralateral primary auditory cortex maps. This suggests that the cortical reorganization also reflects subcortical changes in the representation of the contralateral cochlea [34].

After three months of recovery, newborn kittens with aminoglycoside induced hearing loss show an extensively reorganized primary auditory cortex with almost all units in the region of initial hearing loss tuned to a border frequency between normal and damaged hair cell regions [33]. Substantial reorganization of tonotopic maps in the central nucleus of the inferior colliculus occurs, following sustained neonatal high-frequency sensorineural hearing loss, indicating an overrepresentation of input arising from the high-frequency border of the damaged cochlea [36]. This cortical reorganization has two implications. First, there is an excess of cortical cells representing a very restricted area of the cochlea. Second, the spontaneous and stimulated activity of those cells is likely more synchronized than it was before the damage. The study we now report on was specifically designed to examine the effects of hearing loss induced in juvenile animals on the cortical topographic organization in the adult animal.

Methods and Results

In order to introduce a high frequency hearing loss, kittens were exposed in an anechoic room for one hour to a 6 kHz pure tone presented from a loudspeaker 50 cm away from the animals resulting in 126 dB sound pressure level (SPL) at the kitten's head. During this exposure the animals were awake, confined in a small cage and facing the loudspeaker. The first exposure was at 5 weeks after birth and was repeated one week later. Changes in tonotopic maps were examined in 5 kittens. The animals were tested between two and five months after the trauma was induced. For that purpose, a series of

electrode penetrations in primary auditory cortex (AI) along a line perpendicular to the orientation of the iso-frequency sheets was made to establish the sequence of characteristic frequencies (CF) along most of its caudal-rostral extent. The amount of peripheral hearing loss induced by the pure-tone trauma was established by using the threshold of the auditory brainstem response (ABR). Comparison topographic maps and excitatory response areas were obtained in 7 age matched control animals.

The mean ABR threshold shift in the traumatized animals, compared to the mean ABR threshold in the control cats, was between 25 and 35 dB for frequencies above 8 kHz (Figure 1) with a range between -5 and 55 dB. For frequencies below the trauma tone frequency all thresholds were within the range found for the control cats. For higher frequencies, the number of threshold values above the normal range increased. For 12 kHz and higher, all but one threshold value was above the normal range.

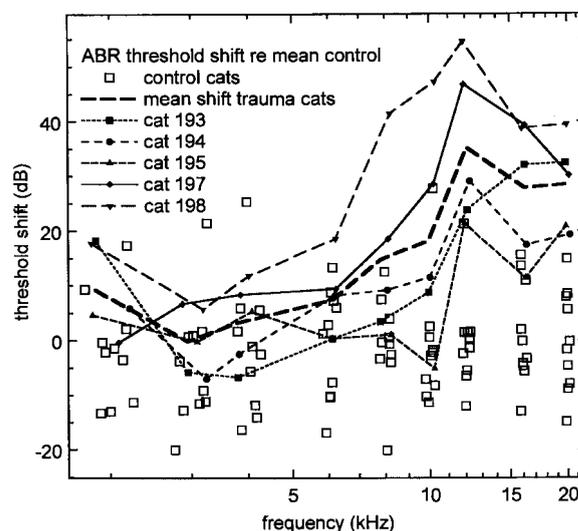


Figure 1 ABR threshold shift in five trauma cats relative to the mean value in seven control cats. The ABR threshold differences from the mean for the control cats are drawn in as well. The mean threshold shift for the trauma cats is drawn in by a heavy dashed line.

Three tungsten micro electrodes with impedances of about 2 M Ω were independently advanced perpendicular to the AI surface to a depth of 700–1200 μ m, likely corresponding to layers III/IV. The electrode positions were plotted onto a Polaroid photograph of the exposed cortex surface and later scanned into PhotoShop[®]. Distance measurements were taken from this enlarged image of the cortical surface. Trigger levels were between 75 and 100 μ V negative on the downward slope of the spikes. The single-electrode recordings always consisted of spikes from more than one unit. These multi-unit spike-trains were separated into single-unit spike-trains [37].

All CF-distance maps in the 12 kittens contained a point close to a CF = 4 kHz, so this was used to

anchor all the other values. The CF was determined for all single units separated from the multi-unit spike trains obtained at each recording site. The CFs of the single units for a particular electrode were generally the same and in the plot (Figure 2) the mean value per recording site was used. The so obtained CF-distance map for the normal cats is very similar to the one presented by Rajan *et al.* [34]. In the tone-damaged cats the highest CFs were about 10 kHz in the litter of 3 kittens and about 7 kHz in the litter of 2 kittens. As a result, the mean CF-distance curve started to deviate from the normal progression at those frequencies, resulting in a 2–3 mm extent of cortex that had essentially the same CF. Thresholds at CF were similar for the trauma- and control animals (Figure 3) and so were the bandwidths of the frequency tuning curves at 20 dB above threshold at CF. Tonotopic order was not preserved in the reorganized region.

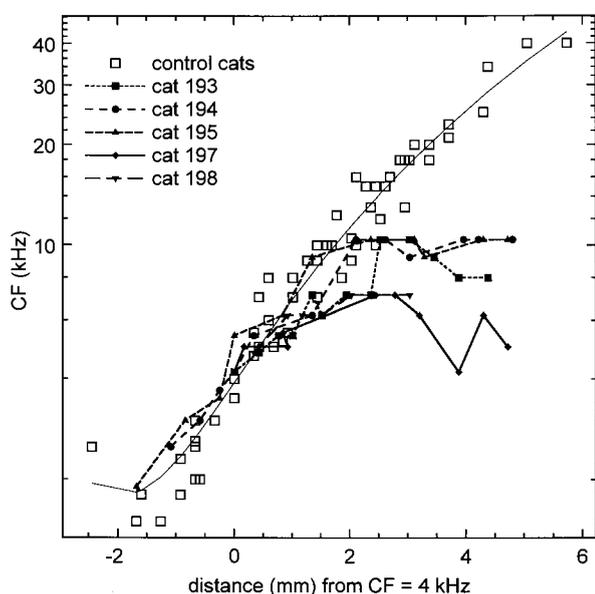


Figure 2 Characteristic frequency (CF) of recording sites as a function of the distance from the site tuned to 4 kHz. The CF axis is logarithmic. The individual data points for trauma cats are connected. A polynomial curve fit is drawn through the data for the control cats.

Spontaneous activity was recorded for a 15-minute period at each recording site. Spontaneous activity (for details see [38]) was significantly higher in the reorganized regions of cortex (mean 2.33 sp/s) compared to the normal regions (break point taken as 6 kHz; mean 1.36 sp/s). For the control cats the mean spontaneous firing rate was 1.31 sp/s and was not significantly different below and above 6 kHz. The spontaneous firing rates in the reorganized region were not significantly elevated beyond the range in the control cats.

Cross-correlograms between neuronal activity recorded on separate electrodes were calculated. The peak cross-correlation coefficient was considered significant if its peak was within 20 ms from the zero-lag point, and its value exceeded the baseline by 3 standard deviations (SD). The peak cross-

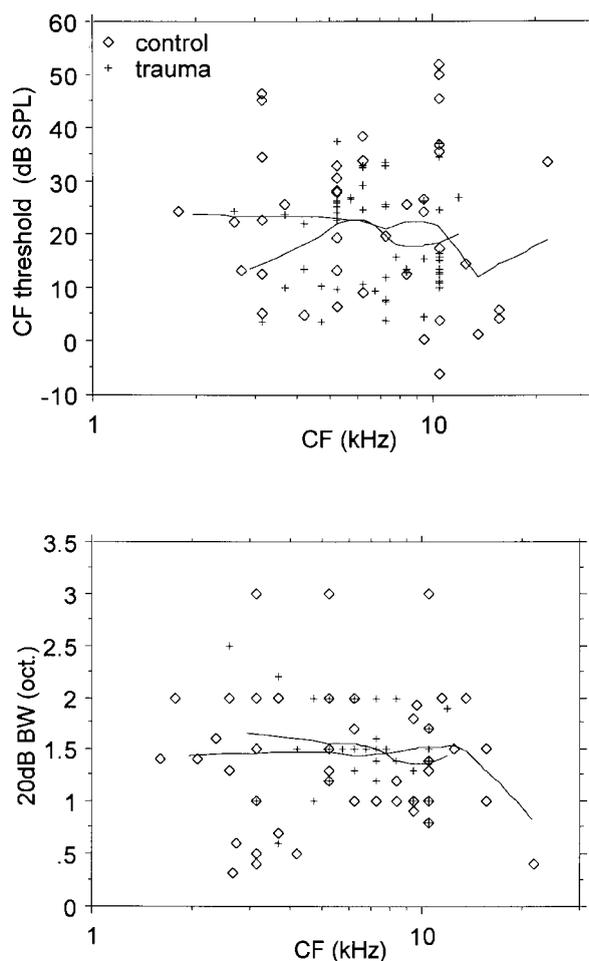


Figure 3 Upper panel: Dependence of threshold at CF on the value of the CF for control and trauma cats. Lower panel: Dependence of frequency tuning curve bandwidth on CF for control and trauma cats. Locally weighted means curves are drawn in, no significant differences are present.

correlation coefficient was evaluated for 140 single-unit pairs recorded in the traumatized cats. A comparison was made with 246 single-unit pairs from the control cats with peak correlation coefficients that were significantly different from zero. The peak correlation strengths were not significantly different for the normal and trauma CF regions (details in [38]). These values were also not significantly different from those in control cats.

Discussion

The finding of normal multi-unit thresholds at CF in the region of hearing loss reflected in the ABR for the trauma cats, combined with relatively large cortical areas with similar CF values strongly suggests a reorganization of the cortical topographic map. In general, changes immediately after the trauma comprise strongly elevated multi-unit thresholds in cortex that are the same as those in the ABR (Kimura and Eggermont, unpublished observations). Thus, over time the units in the CF range of the peripheral damage acquire normal threshold values.

In fact, these threshold values are those of the edge frequency of the audiogram and the CF values are also close to this edge frequency.

These findings may help to understand the consequences of noise trauma acquired at early age in humans. Children in the industrialized world are more and more exposed to recreational noise and as a result may suffer mild to moderate high frequency hearing losses. Our finding of topographic map changes in cat cortex after mild-to-moderate juvenile noise trauma, suggests that such cortical map changes may also occur in these children. Generalization of the findings to humans requires an estimate of the equivalent human age of a 5-week-old kitten. Typically, the properties of neural responses in auditory cortex in kittens are mature between 100 and 150 days of age [39], whereas evoked potential properties in human auditory cortex are mature between 15 and 20 years [40]. This suggests that the cortical maturation in 5 wk old kittens is potentially comparable to that in 5-year old children. Further assuming a similar sensitivity to noise trauma, our data suggest that acquired mild to moderate hearing loss in approximately 5-year old children could result in profound cortical topographic map changes. It is presently not clear if such noise trauma can also induce cortical map changes in adult cats and therefore likely also in human adults.

Cortical topographic map changes in humans have clinical implications: they have among other things been related to abnormal sensations. For instance, a reorganized somato-sensory cortex in amputees may be correlated with phantom pain [41] and, similarly, reorganized auditory cortex is present in patients with tinnitus, an auditory phantom sensation [42]. The observed increase in spontaneous firing rate in the reorganized region of primary auditory cortex found in the present study could be a substrate for tinnitus.

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Average spectrum of auditory nerve spontaneous activity and tinnitus

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The classical experimental mode of inducing tinnitus is administration of high doses of salicylate. The tinnitus so induced is a high frequency noise, it is reversible after cessation of the salicylate administration. One measure of spontaneous activity of the auditory nerve can be obtained by using spectral averaging in silence with a gross electrode. In man such measures have indicated alterations in patients suffering of tinnitus. We have shown in animal experiments that after several days of salicylate treatment the average spectrum increases in amplitude. After cessation of treatment it comes back to its original value. In non-treated animals a similar spectral increase can be induced by presenting an ipsilateral broad band noise of moderate acoustic level which also produces a limited threshold elevation at high frequencies. These spectral modifications are akin, in occurrence, development, reversibility, auditory level and frequency content, to salicylate-induced tinnitus.

Introduction

The availability of objective physiological measures of tinnitus is a necessity for the development of knowledge on pathophysiology of tinnitus. Since by definition tinnitus is an auditory sensation in the absence of a corresponding sound in the external environment, it must correspond for the physiologist to an abnormal spontaneous activity in auditory neural structures. Since most often tinnitus is associated with some irregularities or impairment of the inner ear, it is most likely that the origin of most tinnitus corresponds to some anomaly in spontaneous activity of the eighth nerve. It is well known that the fibers of the eighth nerve, when recorded in optimal acoustic isolation from external sounds in a silent cabin, present a significant amount of spontaneous activity. A debatable question is whether such activity, or how much of it, is induced by internal physiological noise. The quantification of this spontaneous activity constitutes one way of exploring possible physiologic measures of tinnitus. Recordings from nerve fibers in acute physiological conditions, certainly offer extremely precise measures of spontaneous activity which can be analyzed in detail for instance in reference to tonotopic origin and to classes of rates of spontaneous activity. However such recordings require that the animal is

deeply anesthetized which can affect their mode of discharge, the results obtained come necessarily from a limited sample of the whole population of nerve fibers often representing about a few percent. Recordings from a gross electrode on the nerve or very close to the nerve provide another mode of obtaining spontaneous activity of the eighth nerve. These recordings offer the advantage of being obtainable in awake animals avoiding doubts as to the normality of the physiological state of the cochlea, and activities from all fibers contribute to the electrophysiological recordings. As a counterpart precise activities of each fiber are not known. In addition these recordings do not reflect only nerve activity but are influenced by sensory potentials; this can be taken as an advantage for simultaneous exploration of sensory function, but necessitates a variety of experimental controls to ascertain the sensory or neural nature of the recorded signals. After initial exploratory studies a spectral averaging of the spontaneous compound electrophysiological activity of the eighth nerve was presented (Schreiner and Snyder 1987). Further studies using similar recordings were performed by Dolan *et al.* (1990), Martin and Schwegler (1995) and Cazals and Huang (1996). The recorded signals have been given various names, we will use hereafter the acronym ASECA which stands for Average Spectrum of Electrophysiological Cochlear Activity.

Administration of large doses of salicylate is the best ascertained experimental way of producing tinnitus in man (Mongan *et al.* 1973, Day *et al.* 1989). In animals a variety of physiologic studies investigated the effects of salicylate upon auditory nerve activity, small effects were observed with

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recordings from nerve fibers (Evans and Borerwe 1982, Stypulkowski 1990, Kumagai 1992). As for ASECA, in their early experiment on the cat Schreiner and Snyder (1987) showed that a unique salicylate injection increased the amplitude of a spectral peak at 200 Hz. Later studies on humans in peroperative recordings on the auditory nerve from subjects some suffering of tinnitus also presented comparable salience of a 200 Hz spectral peak (Martin and Scwegler 1995, Feldmeier and Lenarz 1996). In humans salicylate is known to induced a high-pitch mild-loudness tinnitus which develops over several days and disappears within days after the salicylate administration is discontinued (Mongan *et al.* 1973, Day *et al.* 1989). A series of elaborate behavioral studies in numerous experiments in the rat (see Jastreboff *et al.* 1994 for a review) gave evidence for the presence a high-pitch, mild-loudness tinnitus developing over days of salicylate treatment. To further explore the physiological significance of ASECA and to assess the validity of changes in ASECA as a reflection of auditory nerve changes induced by salicylate we performed various experiments on control guinea pigs and on guinea pigs undergoing a long-term treatment with salicylate.

Methods

For several years we have been using the technique of chronic implantation of an electrode on the round window of the cochlea in experimental animals as a useful way to monitor cochlear function over months from animals in a normal physiological state. An electrode on the round window allows excellent ASECA recordings as well as recordings of sound-evoked compound action potentials (CAP). All recordings were made in a double wall sound proof room while the awake animal was kept quiet by gently restraining it in a small box. ASECA measures were obtained by averaging approximately thirty seconds of electrophysiological recordings that is about 300 spectrums averaged. A rejection was set to prevent recordings while the animal was unquiet. ASECA and CAP were also recorded in response to various sounds. The acoustic stimuli were delivered through earphones either placed 1 cm away from the pinna or coupled to the external acoustic meatus by a plastic tube. For salicylate treatment, sodium salicylate was injected intramuscularly twice a day, each injection at the dose of 200 mg/kg.

Results

In recordings from the cat and from man a peak at 200 Hz has been repeatedly, but not systematically, observed together with a broad peak at 1 kHz. In the guinea pig only the broad peak at 1 kHz has been observed. In recordings from cat and man a broad peak at 1 kHz is also recorded. Interestingly in cat experiments after injection of salicylate the changes at 200 Hz are accompanied by changes at the broad

peak at 1 kHz. The spectral profile of ASECA in control guinea pigs is shown on Figure 1. From the reference electrode at the frontal cortex is recorded a first peak at very low frequencies, below 100 Hz, which corresponds to the usual electroencephalographic activity. From the active electrode at the round window are recorded a trough around 500 Hz and a broad peak at 1 kHz.

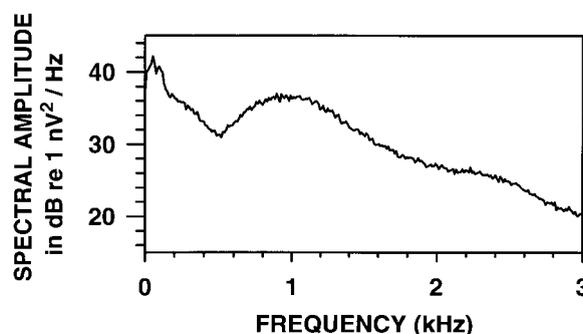


Figure 1 ASECA, Average Spectrum of Electrophysiological Cochlear Activity, from the round window of a control guinea pig.

Physiological significance of ASECA

When various sounds are presented to the ear where ASECA is recorded or to the contralateral ear, different effects are obtained. Schematically, pure tones of 2 to 25 kHz presented to the ipsilateral ear decrease the 1-kHz peak. Pure tones around 16–20 kHz present a threshold for decrease at about 10 dB SPL which is the level of CAP threshold. Since mechanical measurements in the cochlea indicate that pure tones slightly above threshold stimulate a very restricted cochlear tonotopic zone, the 1-kHz peak must originate from a limited zone at the base of the cochlea. Noises with sufficient bandwidths and center frequencies from 4 to 25 kHz presented ipsilaterally produce increases in the ASECA-1-kHz peak. No effect was detected for contralateral pure tones while contralateral noise bands from 8 to 25 kHz reduced the 1-kHz peak. The temporal course of these ASECA-1-kHz peak changes was determined by filtering the electrophysiological signal around 1 kHz, full-wave rectification and temporal averaging. The results appear as compound PST histograms, with onset, decay and offset potentials characteristic of histograms from nerve fibers. The temporal course of decrease by a contralateral noise is similar to the inhibitory effects mediated by cochlear efferents. This decrease was found very much reduced under sedation and suppressed under anesthesia in line with known sensitivity of cochlear efferents to the level anesthesia.

Effects of a long-term treatment with salicylate

Animals treated every day with salicylate showed an acute decrease of the ASECA-1-kHz peak measured in silent conditions, during several hours after each injection. In contrast after several days the ASECA-

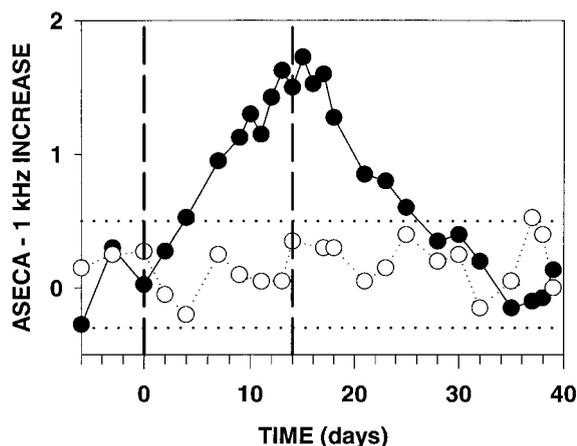


Figure 2 Mean average increase in salicylate-treated animals (black symbols) and in control saline-treated animals (white symbols). Vertical dashed lines indicate beginning and end of treatment. Horizontal dashed lines indicate maximum and minimum of fluctuations in control animals.

1-kHz peak increased progressively over days of treatment. After cessation of treatment the ASECA-1-kHz peak returned to its initial value within several days. The CAP thresholds also monitored during the treatment did not show any change. In control animals injected with saline and monitored in parallel, no change in the ASECA-1-kHz peak was observed. In salicylate-treated animals the effects of a contralateral noise remained unchanged. The increase in ASECA observed in the treated animals could be exactly mimicked in control animals by presenting an ipsilateral broad band noise which also produced a slight CAP threshold elevation at high frequencies. The same noise presented to treated animals just at the end of treatment produced a further increase in ASECA and interestingly produced more threshold elevation than in the control animals.

Discussion

The results of these studies showed that the ASECA-1-kHz recorded in silence peak represents neural activity originating from a limited zone at the cochlear base. Arguments presented elsewhere (Cazals and Huang 1996) indicate that this peak reflects a synchrony of activity between nerve fibers. Results from animals treated during weeks with salicylate (Cazals *et al.* 1998) show that the ASECA-1-kHz peak changes are similar in development, frequency content, intensity level and reversibility to the tinnitus described by humans during treatment with large doses of salicylate. This results point to the ASECA-1-kHz peak as a plausible physiological index of tinnitus. Additional stud-

ies are under development to further document the validity of the ASECA-1-kHz peak to represent tinnitus in different experimental conditions.

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Central activation patterns after experimental tinnitus induction in an animal model

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Subjective tinnitus is a sound sensation in the absence of acoustic stimulation. This phantom sound – audible only to the affected subject – is very variable between people and often changes within individuals over time. Because of a high incidence of disturbing tinnitus in the human population, there is much need for elucidation of the physiological sources of this phenomenon. Manipulations and interventions necessary for a physiological investigation of tinnitus depend on experimentation in animal models. In order for an animal model to qualify for the investigation of subjective tinnitus, above all it is necessary to verify the existence of the phantom sound in the animals. This can be done by comparing observed effects in animals to two ascertained features of subjective tinnitus in humans: (1) perception of tinnitus as a sound and (2) activation of auditory cortex during sensation of this sound [1,2,3]. Therefore, animal models have to fulfill at least these same criteria to qualify as models for subjective tinnitus: (1) It has to be demonstrated that animals perceive a sound during silence – this has been shown in behavioral experiments after eliciting tinnitus with salicylate by Jastreboff [4], and (2) auditory cortex should be active during absence of external sound stimuli – as has been shown with 2-deoxyglucose-mapping, again after using tinnitus-inducing salicylate [5].

Introduction

In high doses, the drug salicylate is a very reliable tinnitus inducing agent in humans, and eventually, tinnitus is used even as an indicator for a therapeutically effective dose of salicylate [6]. Because of a wealth of human data for salicylate as tinnitus inductor it is very close at hand to investigate the effects of this drug on the auditory system in animals. There is general consensus that salicylate has a twofold effect on the auditory system, causing hearing impairment on one side and tinnitus on the other. It is unclear at present how intimately these two phenomena are connected. Current believe is that salicylate exerts its effects on the auditory system through impairing cochlear functions [e.g. 7,8,9], and a number of studies reported salicylate-induced changes in cochlear hair cells [10], in the auditory nerve [7,11,12], or auditory brainstem and midbrain [9,13,14] of different species.

Without exact knowledge of the underlying mechanisms, however, one cannot infer from human data that animals treated with salicylate experience tinnitus and that all changes seen in the auditory system are indicators of tinnitus. They might as well be indicators of the hearing impairment that is also caused by salicylate, or might be

caused by other effects of salicylate as increased respiration, heart beat [9], or by other direct salicylate effects on the brain. Therefore it is important to verify by behavioral tests that animals actually perceive phantom sounds. Most important in this respect were behavioral experiments [4,15] demonstrating that rats had auditory perceptions in a silent environment after having been treated with salicylate. Behavioral experiments, however, cannot reveal physiological characteristics of tinnitus generation and manifestation. Electrophysiology on the other hand can give a detailed impression of the activity of single neurons, but these studies are hampered by the fact that only a tiny fraction of the total neuronal population can be investigated and that one can hardly deduce the tonal quality of a salicylate-induced tinnitus sensation [5]. Therefore, in the auditory system neurons that are involved in generating or processing of the tinnitus signal cannot be distinguished from those that merely reflect changes due to impaired hearing. And moreover, electrophysiological recordings from single neurons or fibers alone do not reveal interplay between different brain structures that may be involved jointly in tinnitus generation. Because of the often tonal quality of salicylate-induced tinnitus in humans and the therefore suspected tonal percept in animals, focal

changes of activity in tonotopically distinct loci along the auditory pathway are to be expected.

A spatial overview of activity in the whole brain can be achieved by methods that map activity in all brain areas in one single experiment as the 2-deoxyglucose method or c-fos immunocytochemistry. Looking at the whole brain is important when studying a phenomenon as tinnitus that might arise at any station of the auditory system, and also might be influenced by non-auditory brain regions. With such mapping studies it is possible to identify structures for further detailed analysis and to identify interactions between brain regions (see Langner and Wallhäusser-Franke, this volume). Since anesthetics may influence neuronal characteristics, a further advantage of these mapping techniques is that the animals are relatively undisturbed during experiments as anesthesia or restraint are not required. Most important in that respect is the finding, that the same anesthetic may cause opposite activity changes in different auditory nuclei, as was shown for agents like nembutal (pentobarbital) or ketamine and mixtures of both, that are commonly used in auditory experiments [16,17]. A further complication when combining anesthesia with salicylate are possible interactions between these drugs which have hardly been considered so far.

With the 2-deoxyglucose method (2-DG), and c-fos immunocytochemistry (c-fos) we could show that salicylate injections lead to activation of the auditory cortex in gerbils [5,18]. Activity in the auditory cortex is even more indicative of tinnitus if – as observed in our experiments – simultaneously activation in the auditory brainstem is suppressed, since this minimizes possible stimulation by external or body sounds. Hence, we assume that salicylate induces tinnitus in the gerbil and, that it does so very reliably if given in sufficient doses [5]. We found that activation in field AI of auditory cortex by salicylate was not diffusely distributed, but was concentrated in narrow bands where neurons are tuned to the same best frequency [5]. Comparison with 2-DG patterns in auditory cortex after sound stimulation [19] revealed that bands of increased 2-DG incorporation observed after salicylate injections run along isofrequency bands. Position and number of these bands varied between individuals, but their orientation and spatial extents suggested that neurons with specific spectral properties were selectively activated – probably causing phantom sensations resembling the percept of a simple sound composed of few pure tones [5].

In addition to using different doses of salicylate to induce tinnitus, we also used impulse noise as a another means to evoke tinnitus in gerbils. From reports on human cases it is evident, that persistent or transient tinnitus often arises after incidences of impulse noise like exposure to firecrackers or shotguns. Our aim was to compare activity patterns resulting from these different treatments in order to find joint characteristics that would be good candidates of tinnitus-related activity changes in the auditory system.

Materials and methods

Experimental tinnitus induction

Tinnitus was experimentally induced in young adult mongolian gerbil (*Meriones unguiculatus*) of both sexes either through injections of sodium salicylate or by firing off a toy pistol. Sodium salicylate (Sigma) was dissolved in sterile saline so that the gerbils received approximate injection volumes of 0.5 ml. Gerbils received one (c-fos) intraperitoneal injection or one injection per day on 4 consecutive days (2-DG) and stayed in their homecages thereafter. Five (2-DG) to seven (c-fos) different doses of salicylate ranging from 0 mg salicylate (saline control) per kg bodyweight (b.w.) to 350 mg/kg b.w. were injected with 4–6 animals per dose.

Other gerbils were exposed to impulse noise caused by firing off a toy pistol loaded with commercially available ‚amunition‘ close to each ear of a gerbil, with loudness reaching 105 dB. 2-DG or c-fos experiments were performed 0, 1, 3, 5 or 7 hours afterwards with about 3 gerbils per time point and technique. For the c-fos experiments, an untreated gerbil served as a control.

2-deoxyglucose (2-DG)

Experimental procedures during 2-DG sessions, sectioning, preparing of autoradiographs and pseudo-3D reconstruction of the cortex essentially followed the routine described earlier [5]. Two hours after the last salicylate or saline injection, or 0, 1, 3, 5 hours after having been exposed to impulse noise, awake animals were injected intraperitoneally (i.p.) with 18 μ Ci of 2-deoxyfluoro-D-(U-¹⁴C)glucose (2-DG; Biotrend) in 0.2 ml sterile saline. Animals were placed singly in a glass tank with carpet-lined floor, to reduce noise of movements, in a soundproof chamber and remained there for 90 min in the dark in silence. Thereafter, they received an overdose of anesthetic, brains were removed and frozen immediately. For best visualization of activity patterns in cochlear nucleus, inferior colliculus and auditory cortex, it was essential to section brainstem and midbrain in the transversal plane (20 μ m), and the auditory cortex in the horizontal plane (40 μ m). Sections were immediately dried on a hot plate and exposed to Kodak NBM film. Autoradiographs of relevant brainstem- and cortex-sections were recorded with a video camera and processed with Adobe photoshop. Cortical hemispheres were reconstructed by overlaying consecutive sections so that only the cortex remained visible using the rostral tip of hippocampus as a reference line for rostrocaudal alignment.

c-fos immunocytochemistry

Gerbils were separated and housed singly the day before the experiment. Three hours after the i.p. injection or 1, 3, 5 or 7 hours after having been exposed to impulse noise, they received an overdose of hypnodil and were perfused with a mixture of 4%

paraformaldehyde, 0.1% glutardialdehyde in 0.1 M PBS (pH 7.4). Experiments were performed simultaneously with two to three gerbils treated with different doses of salicylate or with different delays to noise exposure to achieve most similar conditions during the time between injection resp. noise exposure and perfusion, and for processing of brain tissue. Serial, horizontal sections (40 μ m) were cut on a vibratome. Every other section was processed for c-fos, alternate sections were stained with cresylviolet. For immunostaining, the sections were incubated with a polyclonal c-fos antibody (Santa Cruz, IC-chemicals) for 72 h at 4°C, and processed according to the ABC-method with 4-chloro-1-naphthol (Sigma) as chromogen. Sections were examined under a light microscope, and exact positions and numbers of neurons were determined on a microscope with a motorized stage attached to a computer-controlled drawing device [20].

Results

Salicylate and 2-DG

In the auditory brainstem, cochlear nucleus (CN), superior olivary complex (SOC), and nuclei of the lateral lemniscus (LL) showed high 2-DG uptake in saline controls. CN and LL were only weakly labeled when salicylate doses of 200 mg/kg b.w. or above were given, while activity in the SOC appeared not to be influenced by salicylate administration. The medial geniculate body (MGB) was darker after salicylate treatment but without any clear pattern of activation. Activity patterns in inferior colliculus (IC) and auditory cortex (AC) changed most clearly depending on treatment with salicylate or saline (Figure 1) [5]. In saline controls, we observed high activation throughout the nucleus so that IC would clearly stick out from surrounding brain tissue by its darker label. At times one or two darker, i.e. more active bands were present in IC following the known tonotopy. One of the bands was located in the central nucleus (ICC) at locations of neurons with bestfrequencies of about 1–3 kHz, the other very dorsal band belonged to dorsal cortex of the IC. Low doses of salicylate up to 100 mg/kg b.w. did not appear to change activity within the IC, whereas 200 mg/kg lead to suppression of activity in the ventral portions of ICC where neurons with high best frequencies are located, while 2-DG uptake was comparable to that of controls in dorsal parts of ICC where neurons with intermediate and low best frequencies are found. After injection of 350 mg/kg b.w. activity was suppressed throughout ICC.

Auditory cortex was analyzed from the same animals and was usually found to be quite pale in saline controls, indicative of low activity levels. In contrast, after salicylate injections activity patterns resembling dorso-ventral isofrequency contours as seen after auditory stimulation appeared in primary auditory cortex AI, in the anterior field AAF, in dorsal AI (AId), and in the posterior auditory fields P.

In AI distinct bands of high activation could be clearly discerned, with pattern and number varying between individuals, while labelling was more diffuse in AAF. Bands of increased activity in AI appeared already at doses of 50 mg/kg b.w. but usually with less dorso-ventral expansion. While salicylate injections of 350 mg/kg b.w. always lead to increased cortical activity, this was not always observed at the lower concentrations.

Salicylate and c-fos immunocytochemistry

Salicylate injections lead to increased numbers of immunoreactive neurons in various brain regions of both hemispheres (Figure 2). In comparison, saline controls expressed negligible numbers of labelled neurons in most parts of the brain except for some areas in the dorsal hypothalamus with quite some immunoreactive neurons, and with fewer in IC. In the auditory system, only the auditory cortex showed a clear and dose-dependant rise in the density of immunoreactive neurons (Figure 2). Labelled neurons were found in all known subfields of auditory cortex: in AI, AAF, P, and in ventral fields AV and V of salicylate-treated gerbils, whereas they were virtually absent after saline injections. Salicylate doses up to 100 mg/kg b.w. yielded only slight increases in the number of immunoreactive neurons in AI, and AAF when compared to injections of pure saline, and c-fos-expressing neurons were distributed in all cortical layers. Between 100 and 200 mg/kg b.w. the density of immunoreactive neurons in AI and AAF more than doubled with not much further increase thereafter. At these concentrations highest densities of c-fos-expressing neurons were found in cortical layers III and IV, the border between AI and AAF could be clearly delineated by a decrease of labelled neurons, and densities appeared more or less symmetrical in both hemispheres (Figure 2) [21]. Regardless of the amount of salicylate injected and in agreement with former observations [20], CN and MGB were devoid of immunoreactive neurons, with the exception of few stained neurons that were sometimes found along MGB's caudal rim and in its ventrolateral part after injecting high doses of salicylate [22]. In the inferior colliculus (IC), there was much individual variation without apparent relation to the dose (0–350 mg/kg) administered, and in contrast to other areas quite many immunoreactive neurons were found in ICs of saline controls [20].

Besides auditory cortex, distinctly increased numbers of labelled neurons compared to saline controls were observed in prefrontal, parietal, perirhinal, piriform, and entorhinal cortex which appeared to increase with increasing doses of salicylate. After salicylate but not after saline injections, many immunoreactive neurons were also seen in nuclei of the limbic system like the amygdala. They were present in all major parts of the amygdala, as the medial (MeA), central (CeA), lateral (LA) and basolateral (BLA) amygdaloid nuclei. Density of stained neurons in LA and CeA systematically increased with increasing doses of salicylate with

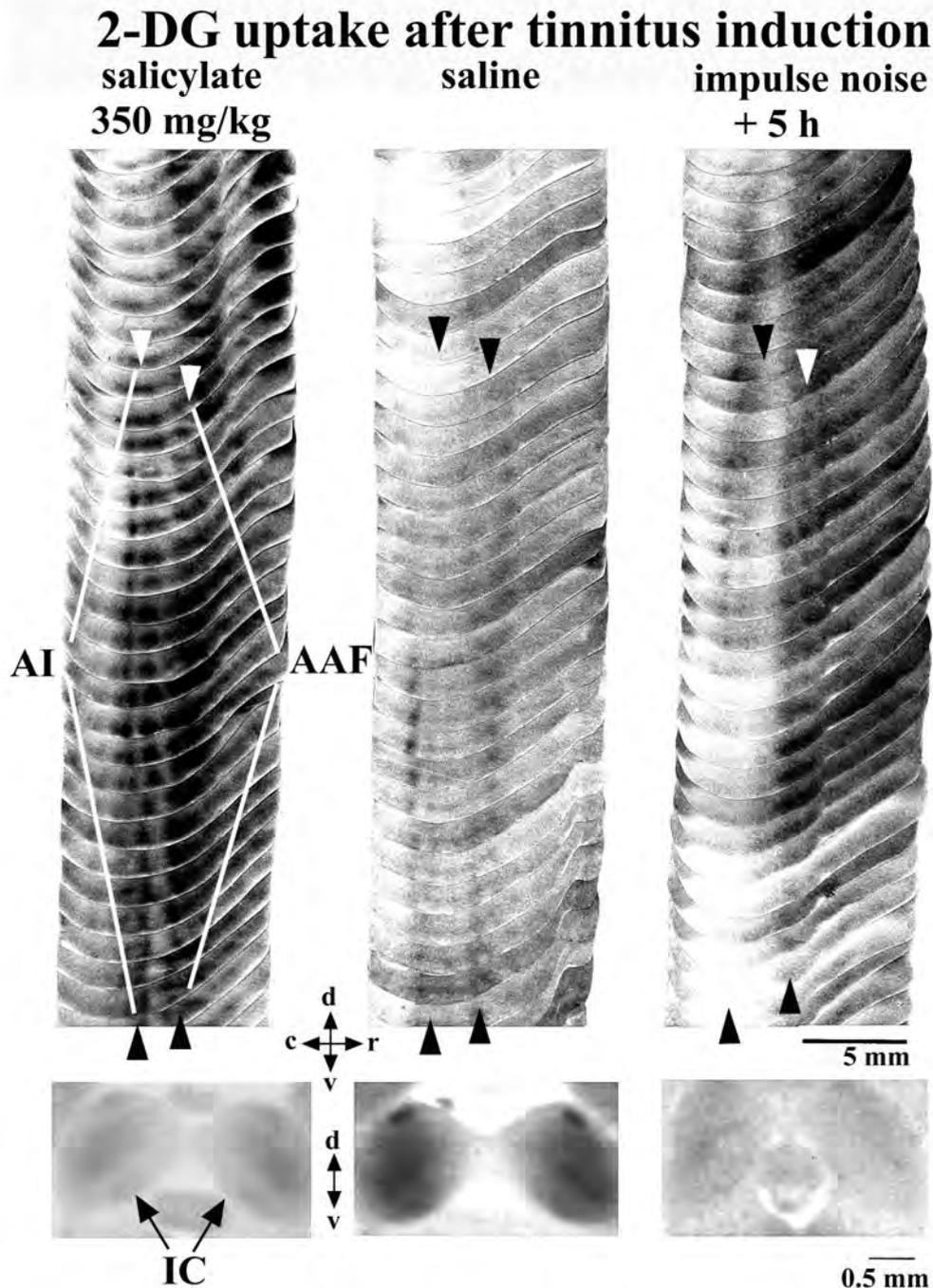


Figure 1 *On top:* autoradiograms of superimposed horizontal cortex sections are shown. Darkness in autoradiograms increases with 2-DG uptake. Fields AI and AAF of the auditory cortex are indicated with arrowheads. Compared to saline controls, 2-DG-uptake in AI and AAF was clearly enhanced along bands according to the tonotopy after injections of 350 mg of salicylate per kg b.w.. Five hours after impulse noise, we still found enhanced activity in AAF. *Below:* autoradiograms from the same animals through IC are shown. Whereas after 350mg/kg of salicylate and after impulse noise we find low activity in IC, saline controls exhibited clearly higher activity levels. c – caudal, d– dorsal, r – rostral, v – ventral.

c-fos expression in auditory cortex and in the limbic system

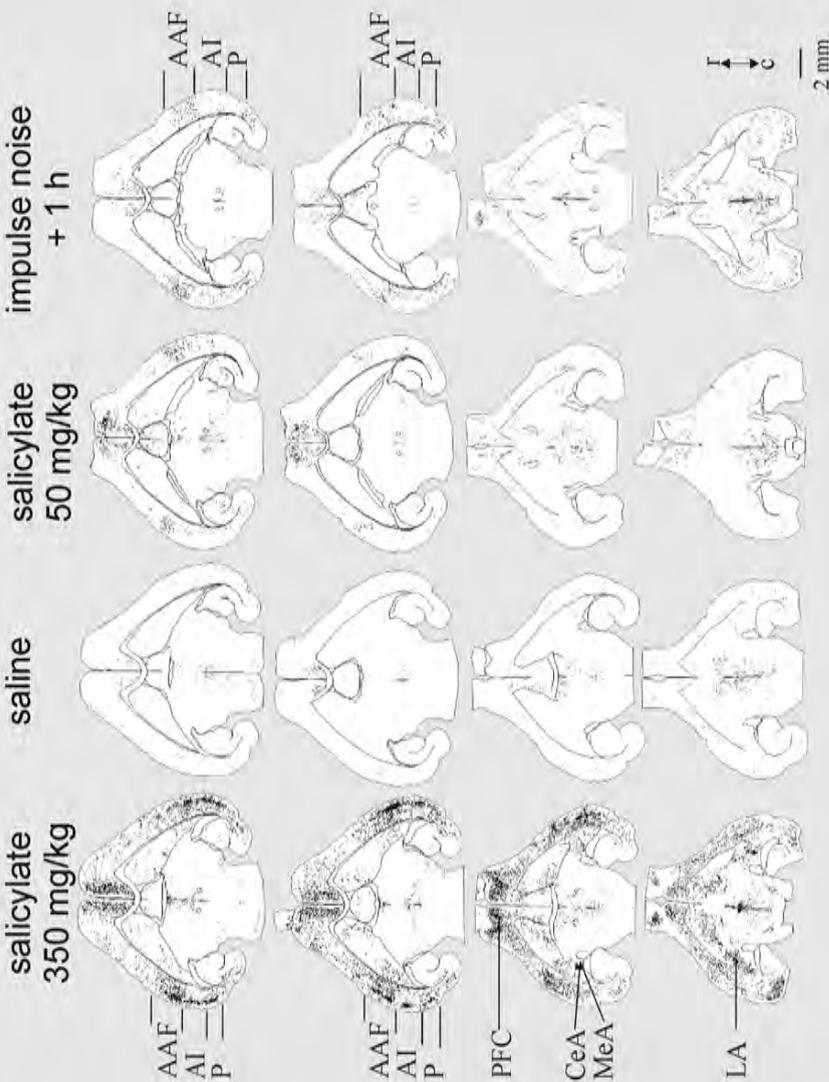


Figure 2 Computer-generated drawings of single horizontal sections processed for visualization of the c-fos protein. Each dot represents an immunoreactive cell. Dorsal to ventral sections are shown from top to bottom. Highest densities are observed after injections of 350 mg salicylate/ kg b.w., and in AI, AAF and P of the auditory cortex as well as in CeA of the amygdala. In auditory cortex we find an accumulation in layers III and IV. Saline controls express low base levels, except in the hypothalamus (lower row). After 50mg/kg of salicylate and 1 hour after noise exposure, densities compared to controls are enhanced especially in AC, PFC, and in the amygdala. For abbreviations see text, c – caudal, r – rostral.

the major increase between 200 and 350 mg salicylate/kg b.w. In CeA, densities reached with 350 mg/kg were higher than those seen in the auditory cortex [21]. Qualitative comparison of brains from gerbils treated with 350 mg salicylate/kg b.w. to saline controls revealed increased numbers of immunoreactive neurons in further nuclei of the limbic system as nucleus accumbens, gyrus cinguli, substantia inominata, lateral septum, in the bed nuclei of stria terminalis, and in subiculum [22]. Many immunoreactive cells were also found in several nuclei along the thalamic midline, and in the hypothalamic medial preoptic area and periventricular nucleus, as well as in several nuclei of the brainstem as locus coeruleus, periaqueductal grey, nucleus of the solitary tract, and in the lateral parabrachial nucleus [20].

Impulse noise and 2-DG

In most cases of impulse-noise exposure it was not possible to suppress activity in the IC bilaterally as much as with the highest dose of salicylate. Often, activity in IC was wiped out only unilaterally and these cases were not considered so far. If we succeeded to reduce activity in IC bilaterally (1 = 1h, 3 = 3 h, 2 = 5 h after noise exposure), we found enhanced activity in the auditory cortex at 1 and 5 hours but not at 3 hours after noise exposure. In contrast to major 2-DG uptake in AI after salicylate injections, darkest labeling after noise exposure was observed in rostral AAF, and in rostrally adjacent parietal cortex (Figure 1). We also found much 2-DG uptake in the prefrontal cortex, and some in DCN but never in ventral cochlear nucleus (VCN) or MGB.

Impulse noise and c-fos

In general, there were fewer immunoreactive neurons at all times after exposure to impulse noise than after injections of high doses of salicylate (Figure 2), and labelling was more confined to auditory and limbic structures and to the prefrontal cortex. Highest numbers of c-fos-expressing neurons were always observed 1 hour after noise exposure, and decreased until 5 hours afterwards. Seven hours after noise exposure we observed distinctly more immunoreactive neurons when compared to values after 5 hours in AAF, CeA, and DCN, in CeA this increase was unilateral [23]. Activity in AI was highest 1 hour after noise exposure, whereas in AAF it was lower at first, but 7 hours after impulse noise the number of labelled neurons in AAF exceeded that seen in AI at this point of time. In auditory cortex, some immunoreactive neurons appeared in clusters but this was not consistently observed, and there was no accumulation in layers III or IV as seen after high doses of salicylate. In the untreated control animal immunoreactive neurons were almost absent in auditory cortex. In the amygdala, many neurons were found at 1 hour in the medial, central and lateral nuclei, whereas activity indicated by c-fos labelling at later intervals concentrated in CeA. We

did not find any c-fos-expressing cells in VCN or MGB, which are usually seen in these regions after sound stimulation (unpublished observations). In IC, we always observed more labelled neurons than in the unstimulated control that, similar to saline controls, expressed a high base level of immunoreactivity. For a detailed correlation analysis of these data see Langner and Wallhäusser-Franke (this volume).

Discussion

Mapping brain activity after experimentally inducing tinnitus with two different procedures revealed two common characteristics: suppression of activity in VCN and IC on one hand, and high activity in the auditory cortex and in limbic regions, especially in amygdala, on the other. This is the first demonstration in an animal model that tinnitus-inducing manipulations lead to cortical activation, a fact increasingly shown for humans [1,2,3]. Suppression of activity in ICC was not always complete, it clearly depended on the dose of salicylate injected, supposedly reflecting different extents of cochlear damage. Possibly, a hearing deficit, albeit slight, is a necessary prerequisite for tinnitus, since one intriguing fact about experimental tinnitus-induction is that these treatments also cause hearing impairment [24]. A correlate of tinnitus, however, must be neuronal activation. Clear activation of auditory structures was seen only in the auditory cortex, in AI and AAF after salicylate injections, and in AAF after impulse noise. After noise exposure, we also observed some minor and inconsistent activation of DCN (c-fos, 2-DG) and IC (c-fos). Since, VCN, receiving its information solely from the auditory nerve was never active, and since activation in the DCN did not correlate with IC-activity, we attribute this to back-projections from the auditory cortex which are known to end in these structures [25,26].

Aberrant excitation of the cochlea, a commonly discussed source of tinnitus, should enhance activity especially in those parts of CN and IC, that are stations of the primary ascending auditory pathway, namely in VCN and ICC. This we cannot confirm with our data, instead activation of the auditory cortex as seen in our experiments, must be generated in the brain itself, and points to a central generation of tinnitus-related activity in the gerbil (see Langner and Wallhäusser-Franke, this volume). Another important aspect of the way we induced tinnitus may be that the animals were exposed to a stressful situation that activates the limbic system simultaneously to changing sensory input into the central auditory system. This could lead to an association between a stressful situation and the auditory percept of tinnitus. A key structure here seems to be the amygdala which endows sensory stimuli with emotional and motivational significance [27,28]. When auditory cortex was activated, we always found correlated activity in the amygdala. There exist direct connections between the auditory cortex and

thalamus and the amygdala [29]. Likely, high levels of salicylate cause physiological stress as indicated by changes in heart rate and respiration, and the sudden experience of impulse noise was an obvious stressor for the animals.

Conclusions

- (1) We assume that reduction of input into the auditory system activates compensational mechanisms in the central auditory system.
- (2) Under influence of the amygdala these mechanisms may induce persistent activation in the auditory cortex.
- (3) This activation is then taken as an auditory percept, the source of tinnitus.

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Brain related potentials, efferent activity and ABRs in chronic tinnitus patients

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Although cochlear dysfunction is a common primary lesion associated with evoking tinnitus, the involvement of central nervous system structures are contingent with the perception of tinnitus as an endogenous chronic and distressing sound. The explorations of the affected site in chronic tinnitus along the auditory pathways are of highly clinical and research values. The aim of this study was to study a variety of brain potentials in chronic tinnitus patients as compared to controls, matched for hearing and age. In addition the activity in the auditory efferent system, as manifested in otoacoustic emissions, was also investigated. Brain potentials were elicited by various auditory paradigms. The results showed that while the peripheral activity, including the OAE and the brainstem potentials, were essentially similar between the groups, all other potentials were significantly altered in tinnitus patients. Primary cortical auditory areas and temporal lobe limbic structures, including the hippocampus and amygdala, have been implicated as the major sources for those potential alterations. The results of these studies provide neurophysiological indices to relate cortical areas, which are crucially involved in detection, perception and memory processes, and the efferent system having essential inhibitory neural activity in tinnitus production. Moreover these results provide some level of objectivity to tinnitus detection which, when coupled with other physiological, audiological and metabolic parameters, may reflect a more accurate description of the tinnitus syndrome.

Methods

A total of 80 male patients aged 26–45 years, suffering at least 5 years from chronic tinnitus were examined. All subjects had documented histories of noise exposures and exhibited variety degree of noise induced hearing loss (NIHL). In order to exclude any major psychiatric disorder, each patient was interviewed and examined by psychiatrist and questionnaires were filled out in order to determine depressive symptomatology. Subjects with major psychiatric disorders were excluded.

ERPs elicited by auditory paradigm

Following EEG electrodes placement, each subject underwent two different auditory paradigm. The first included presentation of 200 stimuli (ISI 2 s, 150 ms duration) of 1 kHz stimuli and the subject was asked to count them mentally. The second test, known as the oddball paradigm for target detection, included 20% of 1 kHz

stimuli serving as targets and 80% of 2 kHz stimuli as non-targets. The subject was asked to press a button only to target and to ignore non-targets. Peak to peak analysis included latency and amplitude measures made for components N1 (70–130 msec) P2 and P3 (the most prominent positive peak after 250 msec).

EEG recordings

Scalp electrodes were placed in the midline sites at Fz, Cz and Pz and temporal placements (T3 and T4). Eye movements were monitored and a special procedure excluded trials with eye movement or blink contamination. A ground electrode was attached to the neck. All recordings were made by an Orgil BPM-30 system. Following amplification (100,000) and filtering (0.1–120 Hz) the epoch of 1500 ms, synchronized to the stimulus presentation were digitized on-line at a sampling rate of 250 Hz per channel.

Suppression OAE effect

Click evoked Otoacoustic Emissions were measured in the absence and the presence of contralateral white noise stimulation at intensities of 5, 15 25, 35 and 45 dBSL.

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Auditory brain stem evoked potentials

The ABEP test was conducted in response to 85 dBHL click stimuli using Cz referenced to ipsilateral mastoid and a ground attached to the contralateral mastoid.

Analysis

Univariate repeated measures analyses of variance (Group × Stimuli × lead), posthoc analysis including corrected t tests were performed.

Results

Figure 1 depicts the auditory ERPs in response to repetitive 1 kHz stimuli for the controls and the tinnitus patients separately. This paradigm elicited a distinct N1 and P2 component. Tinnitus patients were characterized by significant reduced brain N1 and P2 components. N1 amplitude was significantly decreased ($P < 0.002$) in tinnitus patients (in the midline sites 1.7 uV in tinnitus patients compared to 5.9 uV in the controls) and P2 was also smaller in by 60% in the tinnitus group compared to the matched controls. Peak latencies did not change.

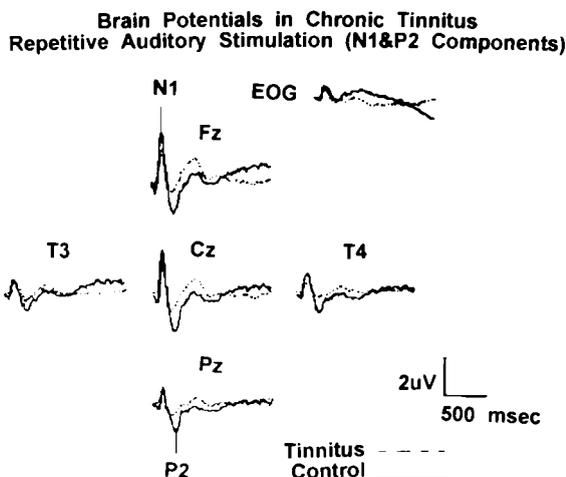


Figure 1 Grand average ERP elicited by a repetitive stimulation of 1 kHz in tinnitus patients and controls

Figure 2 shows the grand brain average ERP evoked by the standard oddball paradigm. As can be seen, tinnitus patients displayed significantly reduced N1, P2 and P3 amplitudes (ANOVA, $P < 0.0001$) across all leads. Again, no significant differences were observed for the peak latencies. The reaction time, measured from the onset of the stimulus presentation up to the pressing button by the subject, was significantly ($P < 0.03$) prolonged by mean of 80 msec duration in tinnitus patients relative to controls. This measure is considered as a behavioral cognitive index, indicating identification of the target stimuli amongst the non-targets.

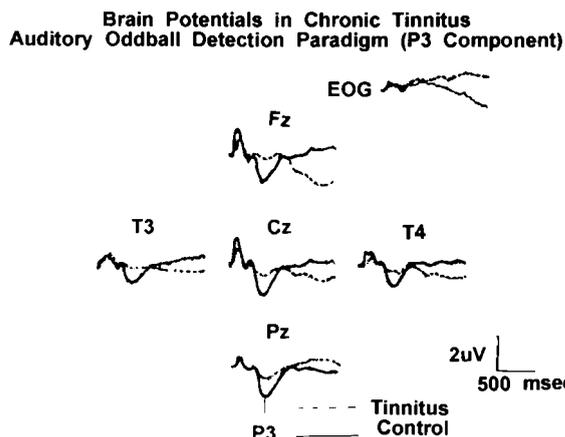


Figure 2 Grand average ERP in response to oddball paradigm for evoking P3, in tinnitus patients and controls

Figure 3 summarizes the results of 80 tinnitus patients whom underwent the suppression test. In tinnitus patients contralateral noise exposure did not result in diminution of CEOAE. The mean responses were found to be significantly different at all intensities ($P < 0.001$). The ABEP peaks (I, III and V) were similar between the groups.

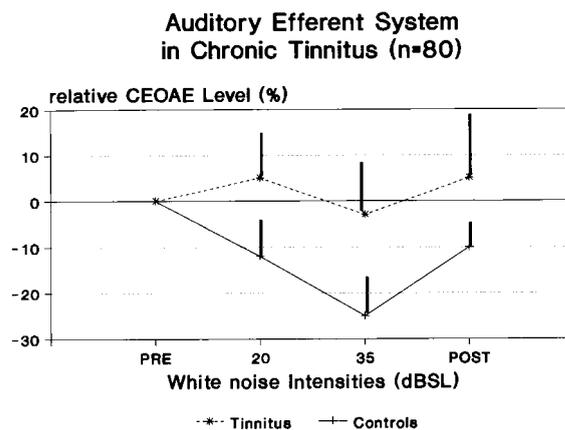


Figure 3 Changes in the mean percentage CEOAE (relative to pre) during presentation of contralateral white noise stimulation in tinnitus patients and controls

Discussion and conclusions

In contrast to insignificant findings in the activation of the cochlea, auditory nerve, and brainstem pathways as reflected in the ABEP and in OAE tests, significant alterations in the brain related potentials and efferent system were found in tinnitus patients for a variety of evoking paradigms as compared to controls.

N1 is presumed to be a sign of an early selection process devoted to the auditory target stimuli. In this view, the N1 decreased in tinnitus patients reflects an impairment in their ability to “tune in” or to have a finely-tuned of auditory input in the early brain processing. The brain processing dis-

order is not restricted only to the early stages of stimulus detection, but is also accentuated in the late and pure perceptual cognitive processes involving stimulus evaluation, memory analyses, and a variety of other brain performance measures. These findings also provide neuro-physiological indications for the cognitive interference frequently associated with chronic tinnitus sensation. Clinical studies using ERP were applied to certain brain diseases or disorders, such as dementia or post traumatic stress disorder, where cognitive impairment is evident [1,2].

The neural origins of the N1, P2 and P3 have not been firmly established, but there are strong indications that the N1 and P2 have a source in the fronto-temporal primary auditory cortex [3]. Direct intracranial recordings, clinical studies and application of three dimensional analysis, strongly pointed to the limbic system and particularly to the outflows of the hippocampus and amygdala (Fornix and Stria terminalis) [4,5] as the major source of the scalp recorded P3. Behavioral studies and clinical evidence from experimental animal model [6] have shown the crucial involvement of both hippocampus and amygdala in discrimination tasks and memory circuits. The changes in the ERP components may suggest alterations in the activation and in the neural inter-relations in those brain areas (Frontal-temporal primary cortex and limbic system) in chronic tinnitus patients. The results of previous study [7] conducted on a similar population showed that this impairment is not restricted to the auditory pathways but could also be observed for visual tasks. Furthermore, the abnormal ERP changes in tinnitus patients are not due to an increased cognitive loading as a result of the tinnitus sound sensation [8].

It seems that the sensory gating in tinnitus patients is essentially different from controls. Sensory gating is defined as an attention-related modulation of the amplitude of stimulus-evoked activity in a sensory pathway or structure without any fundamental alteration in qualitative pattern. This type of attention operates by gating.

Such a gating process could, in principal, be brought about by the efferent projections that modulated either the level of input to the neural population in question or the level of activity within the population itself. With this regard, and knowing the role of the efferent system in modulating the input into the cochlea, the differences in efferent activation between tinnitus patients and controls may elucidate the neural basis of tinnitus.

As this system has demonstrated a suppressive effect, this would suggest that the function of the medial olivary cochlear (MOC) in tinnitus patients is impaired. However, this impairment could also involve the entire efferent auditory pathway, from the auditory cortex to the cochlea. Since the efferent system plays a significant role in both stimulus processing and sensory modulation it seems that tinnitus may be associated with dysfunction of

efferent cortical pathways, as well as in addition to the primary auditory cortex and the limbic system as reflected in the ERPs. Functionally, the whole results strongly support our view that tinnitus involves an impairment of a memory circuit relating to brain information processing.

During the last years significant efforts are made to seek a cortical structural functional or metabolic index related to chronic tinnitus. This includes PET (Positron Emissions Tomography), changes in glucose rate, fMRI and Magnetic ERP (summarized in this volume). Beyond the clinical and academic importance of these attitudes, and beside improvement in understanding the mechanism of tinnitus, they may lead to an objective detection measure of tinnitus. With this regard our results of the efferent test in selective tinnitus patients, induced by noise exposure, are encouraging. We feel that this form of testing will add objective neural information to complement other neuronal measures (ERPs), audiological and behavioral tinnitus measures. Further studies are required. In conclusion, applying a variety of brain functional measures including ERPs, and in the light of the results of the auditory efferent tests, we strongly suggest that tinnitus is a brain informational disorder involving interruption of the primary auditory cortices, the limbic system and the cortical auditory efferent system.

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Tinnitus-related fMRI activation patterns in human auditory nuclei

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Our group is investigating tinnitus using functional magnetic resonance imaging (fMRI) with two main goals: identifying objective measures of tinnitus, and elucidating the underlying pathophysiology. Here, we describe our investigations of lateralized tinnitus which have revealed quantifiable and reproducible abnormalities in fMRI activation. Specifically, we found that a binaural tinnitus masker produced abnormally asymmetric fMRI activation in the inferior colliculi of subjects with lateralized tinnitus. This abnormal asymmetry was attributable to abnormally low activation in the inferior colliculus contralateral to the tinnitus percept.

Two neurally-based models can explain why fMRI activation was abnormally low in the inferior colliculus contralateral to the tinnitus percept. Both assume that the percept is associated with abnormally high (“tinnitus-related”) neural activity in the contralateral inferior colliculus. Additionally, the models assume that either (a) additional activity evoked by sound was limited by saturation or, (b) sound stimulation reduced the level of tinnitus-related activity as it masked the tinnitus percept.

In addition to demonstrating that fMRI can provide (a) an objective measure of lateralized tinnitus, and (b) insights into tinnitus-related neural activity, we discuss how our interpretation of tinnitus-related activation abnormalities provides a conceptual framework to guide systematic fMRI investigations of various forms of tinnitus.

Introduction

This paper reviews our group’s work using functional magnetic resonance imaging (fMRI) to probe the neurophysiology of tinnitus. As illustrated by many of the papers in these proceedings, fMRI is one of several imaging techniques available for probing human brain function, and hence the neurophysiology of tinnitus (see also [1–8]). We chose to use fMRI because: (a) it is noninvasive, showing endogenous changes in local blood oxygenation which are correlated with changes in brain activity [9,10,11] and, (b) it can be used to spatially map brain activation from cortex down to the lowest levels of the auditory pathway with unequalled spatial resolution (e.g., Figure 1 [12,13,14]).

In the following sections, we (a) describe our studies in lateralized tinnitus subjects which have revealed tinnitus-related fMRI abnormalities in the inferior colliculi, (b) interpret the findings in terms of underlying neural activity, and (c) discuss how

the interpretations lead to testable hypotheses concerning the pathophysiology of tinnitus.

Lateralized tinnitus subjects showed abnormally asymmetric fMRI activation in the inferior colliculi

Our fMRI experiments examining individuals with lateralized tinnitus showed quantifiable and reproducible fMRI activation abnormalities in the inferior colliculi in response to acoustic tinnitus maskers [7].

Our approach in these experiments included four main elements. First, we used a masking noise stimulus to change tinnitus loudness and examined the inferior colliculus (IC) for corresponding changes in brain activity. This paradigm was motivated by the fact that fMRI detects differences in brain activity (i.e., “activation”) between conditions (e.g., sound on vs. off conditions), rather than absolute levels of activity [9,10,11]. Second, we targeted a tinnitus subpopulation, specifically individuals with tinnitus lateralized to one ear. The decision to focus on a particular subpopulation was prompted by the idea that more uniform results might be obtained within a given subpopulation with shared

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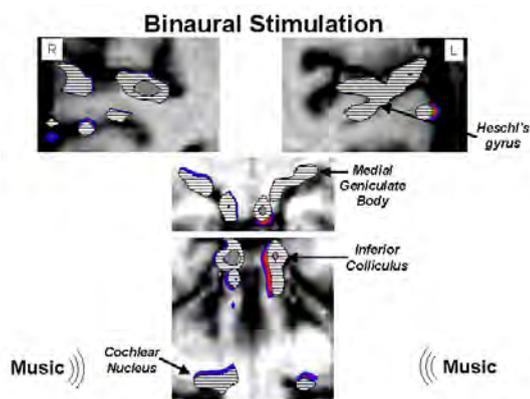


Figure 1 Activation in the cochlear nuclei, inferior colliculi, medial geniculate bodies, and auditory cortices in response to binaural stimulation. The stimulus was orchestral music. Each panel shows an anatomical image (grayscale) and superimposed activation map (hatching) for a slice passing through the cochlear nuclei and inferior colliculi (bottom), the inferior colliculi and medial geniculate bodies (middle), and posterior Heschl's gyri (top). The bottom, middle and top panels each correspond to a different subject without tinnitus. Functional images of one slice (asymmetric spin echo, TE = 70 ms, offset = -25 ms) were acquired every other heart beat and were corrected for fluctuations in interimage interval [12]. A single slice, rather than multiple slices, was functionally imaged to reduce the effect of acoustic scanner noise on activation [15]. The stimulus was repeatedly turned on for 30 sec and off for 30 sec. Activation maps were derived by comparing image signal strength during stimulus "on" vs. "off" periods using a t-test (horizontal and vertical hatching indicate $p < 0.001$ and $p < 2 \times 10^{-9}$, respectively). Each activation map is based on data acquired over 13.5–18 minutes. Imaging was performed using a 1.5T scanner (GE) equipped for echo-planar imaging. Slice thickness: 7 mm. R: right, L: left.

characteristics, than across subpopulations, and this greater uniformity would make it easier to identify tinnitus-related abnormalities. The third component of our approach was to only consider subjects with normal or near-normal audiograms (see Figure 3 caption). This was done to control for inter-subject differences in hearing loss. The final component was to tailor the experimental design to the characteristics of the tinnitus subpopulation under study. For lateralized tinnitus subjects, we hypothesized that sound-evoked activation would be abnormally asymmetric because of the asymmetry of the tinnitus percept. To test this, we compared the degree of activation asymmetry in lateralized tinnitus subjects with that in audiometrically-matched control subjects.

Binaural, broadband noise produced abnormally asymmetric activation in the inferior colliculi of lateralized tinnitus subjects, as illustrated qualitatively by the fMRI activation maps in Figure 2. In control subjects without tinnitus, activation in the left and right IC was comparable. The abnormal asymmetry in lateralized tinnitus subjects was attributable to abnormally low activation in the IC contralateral to

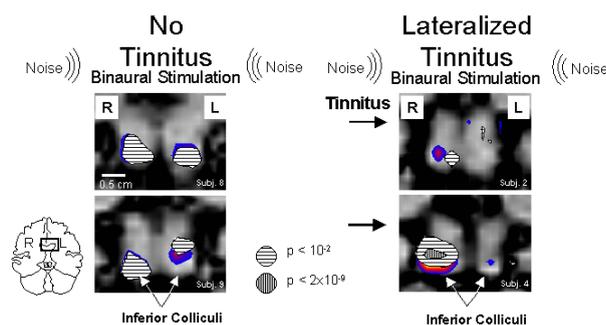


Figure 2 Inferior colliculus activation in response to binaural noise in two control subjects without tinnitus (left) and two subjects with tinnitus lateralized to the right ear (right). Functional imaging was performed as described in the caption for Figure 1, except that the stimulus was continuous, broadband noise. Activation maps are based on a t-test comparison of images during stimulus "on" vs. "off" periods. Each map is based on data acquired over 12 minutes. Area of each panel corresponds to the rectangle on the diagrammatic image at left. Stimulus level was 55 dB re threshold measured in the scanner room. Slice thickness: 7 mm. R: right, L: left. Adapted from [7].

the tinnitus percept (i.e., in the left IC because all of our tinnitus subjects had tinnitus mainly in the right ear).

Lateralized tinnitus subjects were also quantitatively distinguishable from control subjects on the basis of activation asymmetry in the IC. For each subject, an asymmetry index was calculated as the ratio of activation in the right vs. left IC (Figure 3; see caption for details). Since our initial study [7], we have acquired additional data in lateralized tinnitus and control subjects, so Figure 3 includes these, as well as our previous data. The mean asymmetry index for lateralized tinnitus subjects (1.8 ± 0.2 , mean \pm std. error) was significantly greater than that for control subjects (1.1 ± 0.1 ; $p < 0.001$, t-test).

In short, we found that lateralized tinnitus subjects can be reliably distinguished from control subjects on the basis of sound-evoked activation asymmetry in the IC. This indicates that fMRI can provide an objective, physiological measure of lateralized tinnitus.

Tinnitus-related activation abnormalities: relationship to underlying neural activity

We previously proposed the following interpretation for our finding of abnormally low fMRI activation in the IC of lateralized tinnitus subjects [7,16]. First, the tinnitus percept was associated with abnormally elevated neural activity. Second, this "tinnitus-related" activity was distributed as if the lateralized percept had been produced by monaural sound, i.e. greater contralaterally in the IC [7,13,14]. Third, when lateralized tinnitus subjects were stimulated with sound, the resulting fMRI

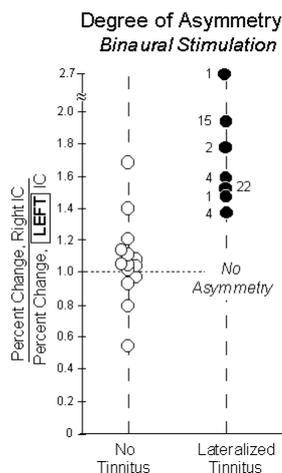


Figure 3 Degree of activation asymmetry in the inferior colliculi of lateralized tinnitus subjects and control subjects without tinnitus. Binaural stimulation. Activation was quantified as the percent change in image signal strength between stimulus “on” and “off” periods. Activation asymmetry was calculated as percent signal change in the right IC divided by percent signal change in the left IC. Each data point corresponds to a particular subject and imaging session. Stimulus level was 55 dB re threshold measured in the scanner room. Value next to each filled circle indicates tinnitus subject number (control subject numbers have been omitted for clarity). Text for the left IC is highlighted as a reminder that the left IC was contralateral to the tinnitus percept in the tinnitus subjects. There are two data points for tinnitus subjects #1 and 4 because these individuals were studied in two imaging sessions on different days. Subjects had normal thresholds (≤ 25 dB HL), normal thresholds for all but one audiometric frequency (30 dB HL) or, a mild, symmetric high- or low-frequency loss.

activation was abnormally low in the IC contralateral to the tinnitus percept for one of the following reasons: (1) Tinnitus-related activity was sufficiently high that any additional activity evoked by sound was limited because neural activity reached a maximum (“saturation model”). (2) Sound stimulation reduced (masked) the level of tinnitus-related activity as it masked the tinnitus percept, but simultaneously evoked an increase in activity in the normal way. This resulted in little change in activity between stimulated and unstimulated conditions (“physiological masking model”). Evidence to support our interpretations of tinnitus-related activation abnormalities is discussed below.

The tinnitus percept and elevated neural activity: previous studies and future tests. The idea that the tinnitus percept corresponds to abnormally elevated neural activity in the auditory pathway is a widely-held view that has support from the animal literature [17,18,19], but direct evidence in humans is sparse. Using positron emission tomography (PET), Arnold et al. showed heightened metabolic activity in the auditory cortex of tinnitus subjects as compared to non-tinnitus subjects [1]. However,

the idea that the tinnitus percept corresponds to abnormally elevated activity in the auditory pathway remains largely untested in humans.

A recent pilot experiment examining the effects of lidocaine on tinnitus-related activation abnormalities in the IC illustrates how the correspondence between tinnitus and elevated neural activity can be further tested in humans using fMRI. The logic behind this experiment was as follows: If the tinnitus percept corresponds to elevated baseline neural activity, completely suppressing the percept should make this activity disappear; baseline neural activity levels would then be normal. In this normal state, sound-evoked fMRI activation would be normal because the elevated activity causing abnormal fMRI activation would have been removed. The methods for this experiment were identical to those of our previous studies of lateralized tinnitus subjects, except that lidocaine, a tinnitus suppressor, was administered partway through the imaging session.

The results of this pilot experiment are shown in Figure 4. Before lidocaine injection, binaural masking noise produced abnormally asymmetric IC activation, replicating our previous results in lateralized tinnitus subjects. Shortly after lidocaine injection, while the tinnitus percept was completely suppressed, the asymmetry disappeared. Later, when tinnitus returned, the asymmetry reappeared. Thus, the activation abnormality was coupled to the presence of the tinnitus percept. This result is consistent with the interpretation that lidocaine reduced elevated neural activity as it suppressed tinnitus, so that fMRI activation became normal.

This experiment demonstrates the feasibility of using lidocaine and fMRI to investigate whether there is a correspondence between tinnitus percept and elevated activity. Since structures throughout the auditory pathway can be imaged (e.g., Figure 1), these investigations could examine where, as well as whether lidocaine reverses tinnitus-related activation abnormalities, and thus elucidate where lidocaine acts to suppress tinnitus.

Physiological masking vs. saturation. The available functional imaging data are as yet too sparse to reject or confirm either the physiological masking or saturation models. Nevertheless, it is worth recognizing that the existing data are broadly consistent with a view of tinnitus-related activity increasing and decreasing with increasing and decreasing tinnitus loudness – the key element of the physiological masking model. For example, Lockwood *et al.* reported changes in PET-detected blood flow in auditory cortical areas that paralleled changes in tinnitus loudness induced by oral-facial movements [5]. Giraud *et al.*, also using PET, found that tinnitus induced by eye movements produced cortical activation in auditory association areas [4]. The PET study of Mirz *et al.* used acoustic masking and lidocaine to modulate tinnitus and found greater activity in tinnitus *vs.* no tinnitus conditions in frontal and middle temporal areas [8]. In an fMRI case study of a tinnitus patient, Levine *et al.*

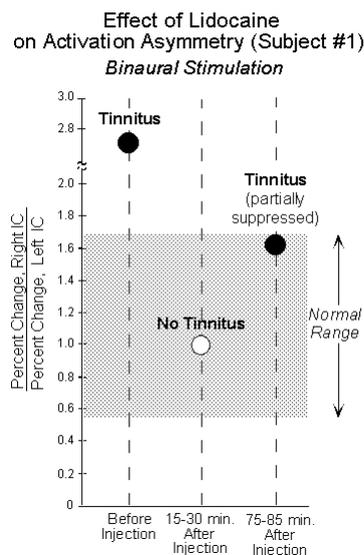


Figure 4 Activation asymmetry in the inferior colliculus in a lateralized tinnitus subject before and after intravenous lidocaine (100 mg over 10 minutes). The stimulus was binaural, broadband noise. The subject turned a knob to indicate tinnitus loudness on a 0/10 (no tinnitus) to 10/10 (maximum loudness ever) scale (as did all tinnitus subjects studied). Before injection (tinnitus loudness 8/10), the asymmetry index was “abnormal”, exceeding the maximum for control subjects. 15–30 minutes after injection during complete tinnitus suppression (0/10), activation asymmetry fell within the normal range. This “normalization” occurred because activation in the IC contralateral to the tinnitus percept increased. 75–85 minutes after injection, during only partial tinnitus suppression (3–4/10), activation asymmetry was at the upper end of the normal range. The subject selected for this experiment (a) had tinnitus lateralized to the right ear and normal audiograms, (b) showed abnormally asymmetric IC activation previously, and (c) had complete suppression of tinnitus with lidocaine during a prior clinical evaluation. Gray shading indicates range of asymmetry indices for control subjects from Figure 3. This experiment, as well as the others described here, were approved by the appropriate institutional committees on the use of human subjects.

reported a decrease in activity in auditory cortex in response to sound (a tinnitus masker), rather than the normal increase [6]. This observation is readily explained by the physiological masking model in which tinnitus-related activity co-varies with tinnitus loudness, but not by the saturation model [7]. Thus, a model in which tinnitus-related activity increases and decreases with tinnitus loudness provides a parsimonious explanation for the available cortical functional imaging data in tinnitus subjects, in addition to providing a possible explanation for our data in the IC (see also [16] in this volume).

A framework for studying different forms of tinnitus using fMRI

The relationship between neural activity and fMRI abnormality proposed above for lateralized tinnitus

can be readily generalized to tinnitus with various “auditory” characteristics. Our interpretations for lateralized tinnitus incorporated the idea that tinnitus-related neural activity is spatially distributed in the auditory pathway as if the tinnitus percept were produced by an analogous sound (monaural sound for the case of lateralized tinnitus). It then followed that fMRI activation in response to actual sound would be abnormal wherever there was tinnitus-related activity. Applying similar logic to tinnitus localized to both ears, for example, one would predict abnormal fMRI activation bilaterally. Applying it to “tonal” tinnitus, one would predict abnormal activation localized to a narrow tonotopic range corresponding to the tinnitus pitch. Predictions can thus be formulated for various attributes of the tinnitus percept – predictions that can be tested through fMRI experimentation.

An intriguing possibility is that the predictions just outlined might be borne out in some tinnitus subjects but not in others, suggesting that tinnitus-related activity in the auditory pathway or the mechanisms leading to fMRI abnormalities might be linked to non-auditory tinnitus characteristics as well as auditory ones. For instance, we might find that among subjects with similar tinnitus percepts, some show fMRI abnormalities that conform to the above predictions while others do not. A logical step would then be to see whether the physiological differences between these subjects correlate with non-auditory attributes of tinnitus such as the degree of tinnitus-related distress, somatic influences on tinnitus [20], or etiology. If correlations were indeed identified, the physiological underpinnings of a wide range of tinnitus characteristics might then be clarified.

Conclusion

In overview, our fMRI studies in lateralized tinnitus subjects, and the interpretation of our findings, illustrate the methodological and conceptual framework for our on-going fMRI investigations into the pathophysiology of tinnitus.

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Changes of metabolic glucose rate in the central nervous system induced by tinnitus

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The metabolic changes in the central nervous system (CNS) of patients suffering from tinnitus were investigated using ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET). 25 patients were examined and compared to healthy subjects. The patient group with tinnitus showed a marked hypometabolism in several non-auditory areas: the posterior parietal cortex on both sides, predominantly on the right side, the anterior parts of the insula/frontal operculum bilaterally and the posterior part of the anterior cingulate cortex could be detected as areas of decreased activity in tinnitus patients. There were no statistical significant increases of relative regional glucose utilization in the study.

These results demonstrate that tinnitus patients show a marked hypometabolism in cortico-limbic structures of the CNS. This modified activity shows a neural adaptation in tinnitus patients. The adaptation pattern in several distinct brain areas is comparable to that of pain and gives evidence for a similar processing and perception of tinnitus.

Introduction

Different cochlear dysfunctions including middle-ear infection, otosclerosis, Meniere's disease, sudden hearing loss and noise-, age- and ototoxicity-related hearing loss can be accompanied by tinnitus. Thus, tinnitus is not a disease but a symptom associated with varying cochlear disorders. Although in most cases the disturbed cochlea is widely accepted as the etiological factor of tinnitus, the location of the pathophysiology responsible for perceiving tinnitus is still under discussion. As most tinnitus patients have some degree of hearing loss that can be related to hair cell damage, it is reasonable to assume the cochlea as the 'tinnitus generator'. On the other hand central components seem to be important in the perception and processing of tinnitus, too.

Modern imaging techniques offered first results to identify brain areas involved in tinnitus perception: Tinnitus patients showed an asymmetry in the activity of the primary auditory cortex revealed by ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) [1]. Changes in the loudness of tinnitus is accompanied by an activation of the

auditory cortex as well as of limbic structures [2]. In addition, the tonotopic organisation of the primary auditory cortex seems to be disturbed in tinnitus patients [3]. These first data demonstrate that tinnitus results not only in activity changes in auditory areas but in several parts of the CNS.

The aim of this study was to investigate the pattern of regional cerebral metabolic rate of glucose (rCMRG) of tinnitus patients with emphasis on non-auditory areas like the limbic system.

Methods

Subjects

Twenty-five tinnitus patients (10 females and 15 males, mean age 49.2 ± 13.2 years) and 20 controls free of tinnitus and neurological disease (9 females and 11 males, mean age 35.2 ± 11.5 years) were studied. In the patient group tinnitus was experienced between 3 weeks and 18 years. Standard audiological examination revealed a normal hearing threshold in one patient, mild to severe high-frequency cochlear hearing loss in 15 patients and deafness on the side of tinnitus perception in 9 cases. Deafness was due to removal of an acoustic neuroma in 7 cases, to Meniere's disease in one patient and to neurectomy of the eighth nerve in one case. All patients had normal middle ear function. Tinnitus was reported as continuous high

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pitched ringing in one ear (20 patients) or in both ears or in the head (5 patients). The controls had a complete normal audiologic examination with normal hearing thresholds, normal tympanograms, normal middle ear reflexes and normal speech perception.

In accordance to the declaration of Helsinki, all subjects gave their informed written consent to participate in this study.

Data acquisition and analysis

The positron emission tomography (PET) studies were performed during standard resting conditions (eyes closed and both ears plugged). An acquisition of 30 min were started 30 min after the intravenous injection of 370 MBq ^{18}F -fluorodeoxyglucose (FDG). For observer-independent determination of regional changes the FDG-PET images were analyzed by SPM-96. All images were transformed into a standard stereotactic space [4,5,6] and smoothed using an isotropic gaussian kernel (12 mm FWHM), which accommodates inter-individual anatomical variability and has shown to improve the sensitivity of the statistical analysis [7]. The global cerebral glucose metabolism was normalized to the global mean with analysis of covariance (ANCOVA) [8]. A group versus group comparison was performed with a t-statistic. The resulting statistical parametric map was transformed to a normal distribution, SPM $\{Z\}$ and foci of significant differences were then characterized in terms of spatial extent (κ) and peak height (μ). The critical level of significance was set at $p < 0.05$ for a combined cluster and height response corrected for multiple comparison in the whole brain volume. Focussed search was done in the auditory cortex [9] and cortical areas with connections to limbic areas (Hippocampus, insula, amygdala) based upon previous reports [10,11,2]. According to the reported similarities between pain and tinnitus [12], pain related structures of the CNS (anterior cingulate cortex [ACC], posterior parietal cortex [PPC], insula, thalamus and posterior cingulate cortex) were included in this focussed search [13,14,15]. Within these predefined regions the probability threshold of μ was set at $p < 0.001$ (not corrected for multiple comparison).

Results

The statistical analysis of the group versus group t-statistic revealed significant tinnitus specific decreases in regional cerebral blood flow (summarized in Table 1).

Surprisingly, the auditory system did not show any statistical significant difference between patients and controls even at lower probability thresholds. In contrary, non-auditory areas like the PPC and the anterior part of the insula exceeded the critical threshold of significance bilaterally. The PPC showed bilaterally the highest significant deviation (Talairach coordinates for the maximum significant voxel x/y/z, right side: 50/-38/50; z-score, 4.54; left side: -48/-48/56; z-score, 3.95). This was followed by bilaterally decreases in rCMRG in the anterior part of the insula (right side: 52/14/2; z-score, 4.36; left side: -46/16/-4; z-score, 4.35). The cluster in the anterior part of the insula extended to the region of the frontal operculum bilaterally. The metabolic changes in the posterior part of the ACC were above the defined threshold for predefined regions, but below the more conservative global threshold corrected for multiple comparisons. The extent (κ) of the hypometabolism in the posterior ACC was considerably smaller than in the PPC and insula (Table 1). All other predefined regions did not exceed the defined threshold.

There were no significant increases of activity above the predefined threshold in this study.

Discussion

As we compared the normal activity status in the CNS of tinnitus patients with that of healthy subjects, we expected to reveal neural substrates of neuroadaptation to the symptom tinnitus. Several primarily non-auditory areas showed significantly decreased activity: the posterior parietal cortex bilaterally and the anterior part of the insula bilaterally. In addition, the ACC also showed decreased bilateral activity although not significant at the p-value corrected for multiple comparison. We could not detect any significantly increased

Table Statistical group analysis of tinnitus patients versus control subjects

| Region | BA | Coordinates x/y/z | z-Score, μ | extent, κ | p-value |
|---|----|-------------------|----------------|------------------|---------|
| PPC, right | 40 | 50 / -38 / 50 | 4.54 | 702 | 0.018 |
| PPC, left | 40 | -48 / -48 / 56 | 3.95 | 648 | 0.030 |
| Insula, anterior, right/frontal operculum | 47 | 52 / 14 / 2 | 4.36 | 441 | 0.034 |
| Insula, anterior, left/frontal operculum | 47 | -46 / 16 / -4 | 4.35 | 526 | 0.035 |
| ACC | 24 | 0 / -4 / 46 | 4.00 | 221 | 0.110 |

Notes: Significant differences in regional cerebral metabolic rate of glucose (rCMRG) to the experience of tinnitus (patients-control subjects) are listed according to statistical significance and corresponding anatomical regions. The Brodman Areas (BA) show the areas of contiguous voxels of the identified peak activation. The coordinates correspond to the localization of the peak activation in the Talairach atlas; minus is left, posterior and caudal. All Z scores denote an increased response in the control group compared to the tinnitus group. The p-values are given as corrected values for multiple comparison.

PPC, posterior parietal cortex; ACC, anterior cingulate cortex.

activity in this study. This was not expected, as the report from Lockwood *et al.* [2] demonstrated increased activity in the primary auditory cortex induced by altering the tinnitus loudness. These different findings might be due to several reasons: compared to our resting state study with FDG, Lockwood *et al.* [2] performed an activation study using ^{15}O water. Thus, increased activity might be missed in our study as we did not activate the tinnitus perception in any way. Secondly the tinnitus patients studied in our study differed considerably in their hearing loss: most patients had a mild to severe high frequency hearing loss. We also included patients with unilateral deafness and with normal hearing thresholds. Therefore a possibly increased activity might be not statistical significant due to the heterogeneity in hearing loss of the investigated tinnitus patients. Finally increased activity might be missed just because of the spatial resolution of the technique and the analytical approach used in this study.

The significant findings in our study were related to decreased activity in non-auditory areas: the PPC, anterior part of the insula and the ACC. The only report investigating the neural activity in the CNS in tinnitus patients [2], although focussing on the auditory system, demonstrated an activation in the hippocampal area, anterior portion of the temporal lobe and insula. The authors link the activation of the hippocampus to the emotional impact of tinnitus. Our results of decreased activity in cortico-limbic structures, are consistent with these findings. Limbic structures have been suggested to be involved in tinnitus processing [16]. Our study support this hypothesis and extend it to a distributed network of cortico-limbic structures involved in tinnitus.

The combination of PPC, anterior part of the insula and ACC has parallels to findings in patients with chronic pain:

Activation of the PPC has been demonstrated in recent PET studies on both experimental [13,17] and pathological pain [18] as well as in the unpleasant itch [19]. The PPC is part of the posterior attentional system which has close anatomical connections to the anterior attentional networks and to arousal/vigilance systems [20], thus orientating subjects to the sensory input. Hsieh *et al.* [18] suppose that activation of the PPC may reflect, in part, hypervigilance/superattentiveness to the sensory information which accompany the chronic ongoing neuropathic pain.

Bilateral activation of the anterior insula has been reported in experimental acute phasic pain studies [13,14]. The anterior insula, a polymodal convergence area, has main connections with the primary and secondary sensory cortex, the PPC, orbitofrontal, temporopolar and olfactory cortices, anterior cingulate and parahippocampal gyri, thalamus and amygdala [21]. These regions are implicated in sensory-discriminative and affective-motivational dimensions of noxious painful events. Given its strategic anatomical connections, the insula has been suggested to relay sensory informa-

tion into the limbic system. In addition, the insula seems to be important for normal auditory processing [22]. Our findings of an involvement of the insula in tinnitus processing correlates with those of Lockwood *et al.* [2] which demonstrate this region to be affected by tinnitus.

The posterior part of the ACC was detected as an additional region of decreased activity in our study. Several reports on pain processing have reported the involvement of the ACC [13,14,15,17,23,24]. ACC together with the thalamus are the most consistently activated region in pain studies. The ACC, as a defining structure of the limbic system, has been proposed to participate in processing the affective component of the pain experience [25]. This is underlined by the recent study of Tölle *et al.* [15], which linked the encoding of pain unpleasantness to the posterior sector of the ACC.

Taken together the involvement of PPC, anterior part of the insula and anterior cingulate cortex in the processing and perception of tinnitus has, at least in part, parallels to observations in chronic pain patients. This is further evidence for the earlier supposed similarity between pain and tinnitus [12,26]. Moller [12] raises the question, whether tinnitus might be due to the activation of brain areas other than those normally activated by sound. Our results confirm these suggestion and extend it in that way that possibly similar areas of the CNS are involved in the perception and processing of tinnitus like in pain. The fact that activity in auditory areas are not significantly increased in this study suggests that neuroadaptation in tinnitus patients occurs primarily in the reported cortico-limbic structures and not (or to a smaller degree) in the auditory system.

The distributed cortico-limbic areas reported in this study indicate the complexity of central mechanisms for the experience of tinnitus in humans and may reflect the neuronal basis of the psychological component of the symptom tinnitus.

Conclusions

Tinnitus patients show a marked hypometabolism in cortico-limbic structures of the CNS. This modified neuronal activity of the described areas in patients with tinnitus could be evidence for a distributed processing in the human CNS, comparable to that of pain, responsible for the perception of tinnitus.

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Positron emission tomography identifies neuroanatomical sites associated with tinnitus modified by oral-facial and eye movements

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Positron-emission tomography (PET) was used to map brain activity in patients who could modulate the tinnitus loudness by oral-facial movements (OFM). OFM produced significant activity changes in the auditory cortex contralateral to the ear that tinnitus was perceived in whereas sound stimulation produced bilateral cortical activation; this difference suggests that tinnitus has a central origin. Sound stimulation also produced more widespread activation in tinnitus patients than controls. The abnormal activation produced by sound and OFM in patients suggests that cortical plasticity may contribute to certain forms of tinnitus.

Introduction

Because tinnitus is often associated with damage to the sensory cells and neurons in the cochlea, tinnitus has been thought to be due to hyperactivity in the inner ear [1]. However, most studies have found no change or a reduction of spontaneous neural activity in the auditory nerve of damaged ears [2]. Recently, there has been a growing awareness that some forms of tinnitus might originate within the central auditory pathway [3,4]. One of the most compelling lines of evidence for this comes from patients who have had their auditory nerve surgically transected. Despite the fact that the input from the cochlea is eliminated, many patients experience tinnitus in the deafened ear [5,6]. The inescapable conclusion from these studies is that tinnitus originates centrally. Interestingly, a few patients who have undergone acoustic neuroma surgery develop gaze evoked tinnitus, a unusual disorder in which eye movements away from the central gaze position activates or increases the loudness or pitch of tinnitus [6]. These results suggest that gaze evoked tinnitus results from functional reorganization in the central auditory pathway. We have identified

another unusual group of patients who can regulate the loudness and pitch of their tinnitus through oral facial movements (OFM) [7]. OFM-induced changes in tinnitus can be especially useful for brain imaging studies since one can compare the pattern of neural activity in the same patient under two different conditions, i.e. loud *v.* quiet. Recently, we used positron emission tomography (PET) and ¹⁵O water to detect changes in regional cerebral blood flow in a group of subjects who can voluntarily control the loudness of their tinnitus by OFM [8]. We have also used PET imaging to study the brain regions activated by tone bursts [9].

Methods

A detailed description of the methods used these studies can be found in previous reports [8,10]. Normal hearing subjects (≤ 20 dB HL) were used to assess the effects of the background noise of the PET camera on thresholds and to identify regions of the brain activated by tone bursts (500 Hz and 4000 Hz; 30, 50, 70 and 90 dB HL) [9]. PET imaging was carried out on four patients who could modulate their tinnitus by OFM (jaw clench). These patients had moderate-to-severe high frequency hearing loss (≥ 4 kHz) and normal, low-frequency (≤ 1 kHz) hearing. PET imaging was carried out in a Siemens ECAT915/31R tomograph

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with the inferior image plane aligned with the cantho-meatal line. A transmission scan was performed on each subject followed by up to nine emission scans with ^{15}O water (260 mBq or less) as the tracer of regional cerebral blood flow (rCBF). The first 60 s of emission data following arrival of the bolus of ^{15}O water in the brain was used for image reconstruction and analysis. PET images were converted to Analyze format, edited to remove extracerebral activity, and analyzed by statistical parametric mapping (SPM 95) [11]. Acoustic stimuli (500 ms on, 500 ms off, 50 ms Blackman rise/fall time) were delivered by insert earphones (ER3A). Cabot ear protectors (Model 3000) or Bose Series II Aviator ear protectors were placed over the insert earphones to attenuate background noise. Written informed consent was obtained from all subjects and all procedures were approved by the Human Subjects Committee.

Results

Effect of PET Noise

Hearing thresholds were measured in young, normal hearing subjects in a sound booth (ANSI 1992) and in the PET scanner using identical equipment. The overall noise in the PET camera was 73 dB SPL (re 20 μPa). The maximum octave band noise level was 68 dB SPL at 250 Hz; level decreased at 6 dB per octave above the maximum. To assess the effects of the background noise in the PET facility, we measured thresholds in the PET camera and compared these to thresholds in the audiometric sound booth (Figure 1). When subjects were tested with insert earphones covered by passive earmuffs (Cabot), thresholds were within normal limits from 750–8000 Hz, but were elevated 7.5–12 dB at lower frequencies ($p < 0.01$). When thresholds were measured with insert earphones covered by Bose earmuffs with active noise reduction, thresholds were within normal limits at all frequencies except 250 Hz where threshold was elevated by only 8 dB. Thus, when subjects are tested with insert earphone covered by Bose ear protectors, the background noise in our PET camera has no significant effect on threshold except at 250 Hz (8 dB shift).

Tone stimulation in normal subjects

Most functional imaging studies have employed complex stimuli such as speech and language to assess auditory-cognitive function [12]. However, little is known about the pattern of activity evoked by simple auditory stimuli presented at various intensities. Recently, we used PET to map the response of the auditory system to 500 Hz and 4000 Hz tone bursts presented to the right ear at 30, 50, 70 and 90 dB HL (normal hearing subjects, ≤ 15 dB HL; insert earphones covered by Bose ear protectors) [9]. The 500 Hz and 4000 Hz tone bursts activated a complex neural network that included many components within and outside the classically defined auditory pathway. The major auditory sites

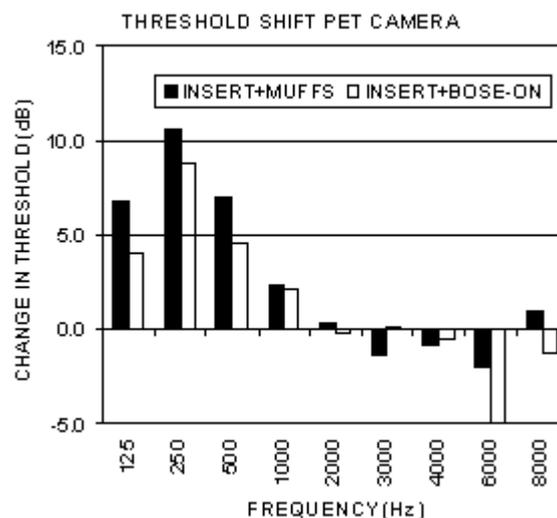


Figure 1 Change in hearing thresholds in the PET camera relative to thresholds measured in an audiometric sound booth. Hearing thresholds measured with insert earphones covered either by passive hearing protectors (Cabot) or hearing protectors with active noise reduction (Bose).

activated by tone bursts included the ipsilateral and contralateral auditory cortex and left medial geniculate. In addition, a large portion of the left auditory brainstem was activated from the cochlear nucleus and superior olivary complex up to the medial geniculate. Areas outside the classical auditory areas included the lateral cerebellum near the parafloccular lobe and, at low intensities, the posterior cingulate cortex (Brodmann area 23). Surprisingly, we did not observe a significant increase of activity on the ipsilateral side of the brainstem.

Significantly, we found that even low level (30 dB HL) stimuli produced statistically significant increases in rCBF. To illustrate the effect of intensity, Figure 2 shows the total number of pixels in the

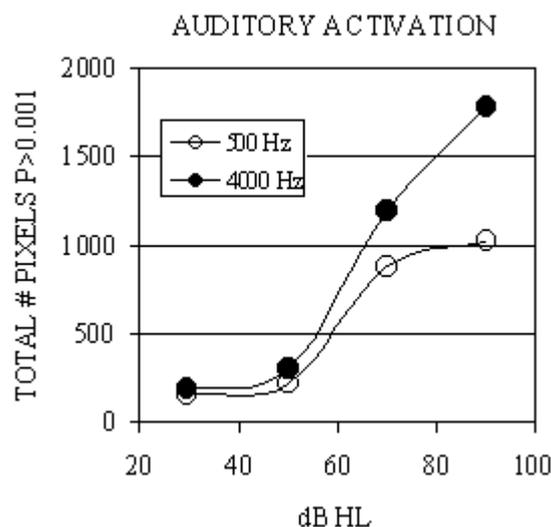


Figure 2 Total number of pixels in auditory sites in the brain that showed a statistically significant increase in CBF relative to the resting state as function of sound level. Data shown for 500 Hz and 4000 Hz.

auditory system (excluding the cingulate) where there was a statistically significant increase ($p < 0.001$) in activity above the rest condition. There are two significant points. First, the total number of pixels exceeding the statistical threshold increased monotonically with intensity with the largest incremental increase occurring between 50 and 70 dB HL. Second, for a given intensity, the number of pixel activated by the 4000 Hz tone was always greater than for the 500 Hz tone. It is important to note, however, that some areas of the auditory brainstem showed maximum activation at the lowest intensity 30 dB HL. Thus, the ability to detect changes in activity in the brainstem requires very low levels of background noise.

Tinnitus patients

PET imaging was carried out on four patients with OFM-modulated tinnitus and moderate-to-severe high frequency hearing loss (30–70 dB HL, >2 kHz) and six normal hearing subjects. Patients had continuous high-pitched ringing in one ear (one, left ear; three, right ear). The pitch of the tinnitus was matched to an external tone near the peak of the hearing loss at sound levels 5–10 dB above threshold (Figure 3). PET imaging was carried out during rest, OFM, and 500 Hz and 2000 Hz stimulation. PET analytical threshold for the SPM analysis was set at $Z = 2.33$, which corresponds to an omnibus $p < 0.01$.

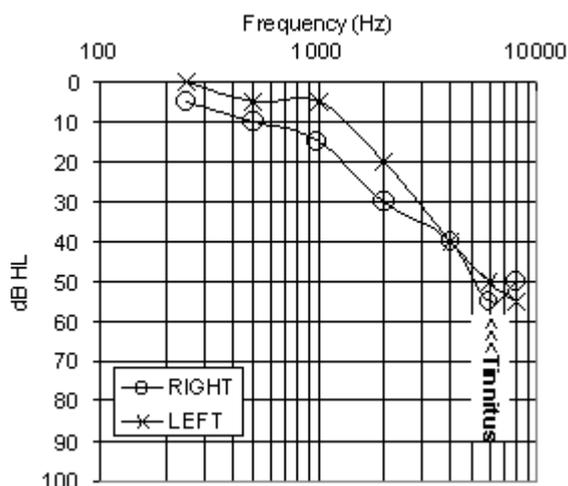


Figure 3 Audiogram for left and right ear of patient with OFM-modulated tinnitus. Pitch of tinnitus near 6 kHz at a level 5 dB above threshold.

OFM-Induced tinnitus

To determine the regions of the brain activated by the OFM, PET images were obtained from patients and controls as they clenched their jaw (data not shown). Analysis of the CBF data for the SPM contrast, normal (OFM – rest), showed a significant increase in CBF in bilateral somatosensory-motor cortex and the supplementary motor area. No

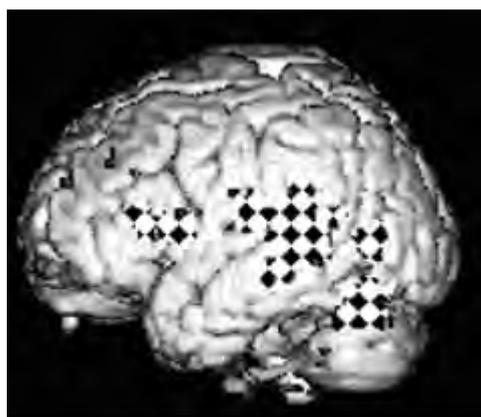
changes were seen in any auditory sites. A similar analysis {patient (OFM – rest)} was performed on two patients who reported a significant increase in tinnitus loudness (data not shown). Significant increases in CBF were observed in somatosensory-motor cortical regions, similar to those observed for control subjects. However, significant increases in CBF were also observed in the left primary auditory cortex (omnibus $p < 0.01$, left superior temporal gyrus, Brodmann area 41) and in a region between the medial geniculate nuclei.

OFM-Induced change in right ear tinnitus

Three patients localized their tinnitus to the right ear. The OFM caused a loudness increase in one patient and a loudness decrease in the other two. Using the appropriate statistical contrast {loudness decrease (rest – OFM) + loudness increase (OFM – rest)} we took advantage of these opposing perceptual effects in the three patients with right-ear tinnitus. Figure 4 shows the regions of the brain that were associated with the change (increase or decrease) in tinnitus loudness. A prominent region of change was seen in the left temporal lobe (Brodmann areas 21 and 41), i.e., contralateral to the ear in which the tinnitus was perceived. Significantly, the phantom sound of tinnitus caused only a unilateral change in auditory cortex. Additional activation was observed in the right thalamus, including the medial geniculate as well as other neural sites (Figure 4).

Stimulation of right ear

To aid in interpreting the data, we presented tone bursts (500 Hz or 2000 Hz) to tinnitus patients and to normal-hearing subjects. In contrast to the unilateral change seen with OFM-induced tinnitus, tone bursts presented to the right ear of patients and controls produced bilateral activation of auditory structures. Tone burst data from patients (Figure 5) showed strong activation in the transverse temporal gyri and adjacent portions of the superior temporal gyri {SPM contrast = (2000 Hz – rest)}. In patients, but not in controls, activation was unexpectedly seen in the left hippocampus. To evaluate the difference between patient and controls in more detail, we performed two additional comparisons. First, we subtracted the activation sites in normal subjects from those in patients during 2000 Hz stimulation {SPM contrast = 2000 Hz (patient – control)}. This contrast (data not shown) revealed excess activity in tinnitus patients in the left hippocampus and the lenticular nuclei. To determine if the differences between patients and controls were due to differences in activity during sound stimulation versus the resting state, we performed a second comparison that eliminated the differences due to the resting state. The statistical contrast in Figure 6 {SPM contrast = patient (2000 Hz – rest) – control (2000 Hz – rest)} revealed greater activation in tinnitus patients in the left primary auditory cortex and anterior portions of the left temporal lobe. This



$z = 8\text{mm}$ {left = right}

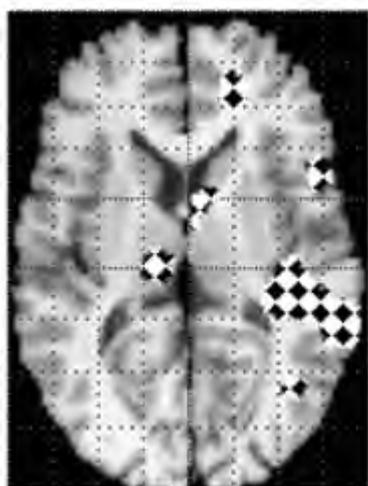


Figure 4 Stippled regions show brain areas where OFM produced a statistically significant ($p < 0.01$) change in CBF in tinnitus patients compared to controls. Top panel shows areas of significant CBF change projected on to the surface of a standard MRI brain image. Bottom panel show areas of significant activation on horizontal sections located 8 mm above the plane of the anterior and posterior commissures. Statistical contrast {loudness decrease (rest - OFM) + loudness increase (OFM - rest)} shows significant unilateral activation in right primary and secondary auditory cortex of temporal lobe plus other extra-auditory sites. Note left-right reversal of image in horizontal sections.

result provides evidence for sound-induced hyperactivity in the auditory cortex of tinnitus patients. However, the contrast did not show any differences between tinnitus patients and controls in hippocampal and lenticular nuclei. Thus, the previous contrast that showed an activation difference in hippocampal and lenticular nuclei may be due to differences in the resting states.

Discussion

If tinnitus in our patients originated in the cochlea, then the pattern of neural activity evoked by OFM-modulated tinnitus should have been similar to that

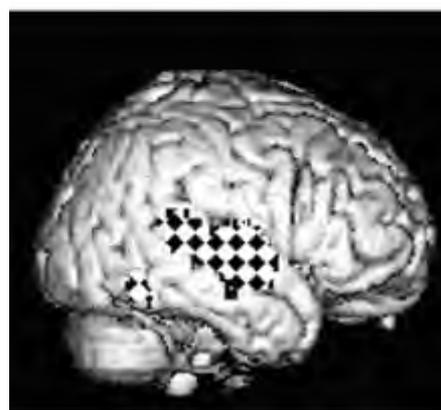
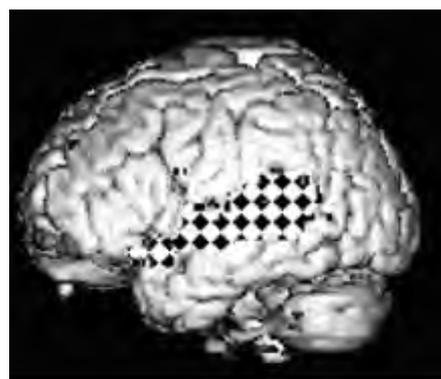


Figure 5 Stippled regions show areas of the brain where 2000 Hz tone burst (right ear) produced statistically significant ($p < 0.01$) increases in CBF in normal controls. Statistical contrast {SPM contrast = (2000 Hz - rest)} shows significant activation in the transverse temporal gyri and adjacent portions of the superior temporal gyri. Top panel and bottom panel show areas of significant activation projected on to a standard MRI brain image. Note significant bilateral activation to unilateral sound stimulation.

evoked by an external sound. Our results show that OFM-modulated tinnitus only produced unilateral activation of the auditory cortex whereas a tone burst that activates one ear caused bilateral activation of the auditory cortex. Since the pattern of neural activity evoked by OFM-modulated tinnitus is completely different from that evoked by a real sound, the inescapable conclusion is that OFM-induced tinnitus originates in the central auditory pathway. This interpretation is consistent with earlier studies showing that tinnitus is present after surgical transection of the auditory nerve [6,13]. Moreover, the tinnitus can be modulated by change in eye position [14,15]. In three of our patients with right ear tinnitus, the OFM activated auditory areas opposite to the ear in which the tinnitus was perceived. Although the sample is small, our preliminary results suggest that tinnitus may originate at neural sites that are contralateral to the ear in which the tinnitus is perceived.

The similarity between tinnitus and phantom limb pain may provide insights into underlying mechanisms. In the somatosensory system, amputation can give rise to phantom limb. Interestingly, the

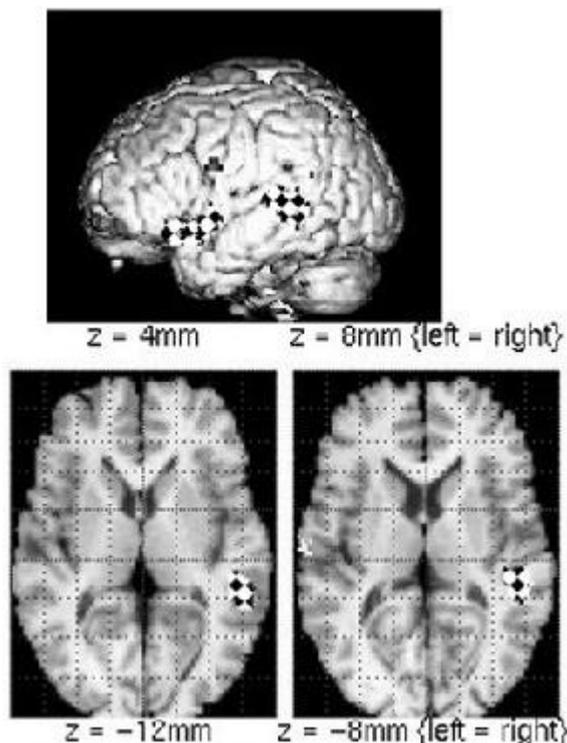


Figure 6 Stippled regions show areas of the brain where 2000 Hz tone burst (right ear) produced significantly greater activation ($p < 0.01$) in tinnitus patients than in controls. This statistical contrast {SPM contrast = patient (2000 Hz - rest) - control (2000 Hz - rest)} revealed greater activation in the left primary auditory cortex and anterior portions of the left temporal lobe in patients versus controls. Top panel shows areas of significant activation projected on to a standard MRI brain image. Bottom panels show areas of significant activation superimposed horizontal sections located 8 and 12 mm below the anterior and posterior commissures. Note significantly greater activation in left temporal lobe of patients versus controls.

severity of phantom limb pain has been linked to the amount of neural reorganization [16]. All of our patients had damage to the peripheral receptors in the cochlea and recent studies have shown that cochlear damage can result in significant functional reorganization in the central auditory pathway. Cochlear damage can cause an increase in spontaneous activity in central auditory nuclei [3]. In addition, many auditory centers become hyperactive to electrical [17] and acoustic stimulation [18–20]. The tonotopic organization of central auditory sites, particularly auditory cortex, is altered by high-frequency hearing loss such that normal frequencies bordering the damaged areas occupy an expanded portion of the tonotopic map. We found evidence of hyperactivity and an expanded frequency representation in our tinnitus patients with high frequency hearing loss (Figure 6). Thus, the changes seen in our tinnitus patients mirror the changes reported in auditory cortex following cochlear damage [21,22].

The mechanisms by which OFM can modulate

tinnitus loudness are currently unknown. However, a reasonable hypothesis is that cochlear pathology leads to reorganization in the central auditory pathway such that functional connections are established with other sensory, motor or emotional centers in the brain. Cochlear damage can lead to the outgrowth of axons in the auditory brainstem [23], alter neurotransmitter release, uptake [24], synthesis and the number of receptors [25]. Thus, many different mechanisms could contribute to OFM-induced tinnitus.

An unexpected finding in patients is that OFM and sound stimulation activated portions of the limbic system, a brain region associated with emotion and memory. Brain lesions induce synapse formation in limbic structures of adult animals [26] and similar changes could occur when the cochlea is damaged [23]. Repeated, high levels of arousal or the negative affect associated with tinnitus may lead to new linkages between auditory and emotional centers and contribute to the emotional impact of tinnitus [27,28]. Intervention strategies that attempt to break these links may reduce the emotional impact of tinnitus.

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Effects of salicylate and quinine on CAP adaptation process

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The effects of systemically applied salicylate or quinine on compound action potential (CAP) adaptation process were investigated in guinea pigs. The threshold of all animals showed 5–30 dB shift about one-half hour after administration of either salicylate or quinine and that of some animals showed recovery during the course of the investigation. Significant changes were found in CAP adaptation process after administration of both salicylate and quinine. These changes might be related to the mechanisms underlying the generation of tinnitus. In addition, abnormal broad N_1 was observed in response to the first click in the click-train after quinine administration. In contrast, CAP response waveforms to the second click and the following clicks in the click-train presented a normal configuration.

Introduction

It is well known that the administration of large doses of salicylate or quinine causes reversible mild to moderate hearing loss and tinnitus in humans. Salicylate administration in guinea pigs caused compound action potential (CAP) amplitude reduction with a recruitment type [1] with relatively minor histological changes such as swelling of the outer hair cells [2]. Quinine administration in guinea pigs caused a threshold shift on CAP input-output function in parallel fashion rather than selectively affecting the low-intensity CAP [1]. Histological examination revealed changes in outer hair cells such as shortening the length [3] and in strial vessel [4].

As has been stated above, salicylate or quinine induced transient tinnitus and hearing loss in humans and probably in animals, these drugs have been used to investigate the mechanism involved in generation of tinnitus. The spontaneous activity at various places along the auditory pathway has been explored because the abnormal firing in the auditory system might cause tinnitus.

We examined the spontaneous firing in cat's primary auditory cortex before and after application of salicylate and quinine [5,6]. The main problem in the evaluation of salicylate or quinine inducing changes in neural activity in animals was that there was no appropriate method to assure that

the animal had tinnitus. The confirmation of the effect of the drug was based on the increase in response threshold. Correlation between the salicylate concentration and behavioral responses indicative of tinnitus was reported and several factors that might exert an influence on these relations were examined [7–10]. These experiments suggested that animals might experience tinnitus after application of salicylate. It has been reported that tinnitus precedes a hearing impairment in humans in response to salicylate administration [11]. If the same holds true for animals, an increase in CAP threshold is supposed to be an important finding predicting the existence of tinnitus. The same method to above mentioned salicylate experiment was applied for quinine. It was suggested that the elevation of hearing threshold was closely related to the quinine blood concentration in guinea pigs [12]. We observed the abnormal synchronization between cortical cells after salicylate [5]. In addition, the same tendency in neural synchronization was also found after the administration of quinine [6]. Considering that our results were similar to those of Eggermont [13] that width of cross-correlograms decreases during sound stimulation compared to that for spontaneous activity, we suggested that changes in Ca^{2+} -channel conductance and free intracellular calcium concentration are likely to be responsible for abnormal synchrony in cortical cells resulting in generation of tinnitus.

As mentioned above, the effect of salicylate and quinine on CAP threshold and more central aspect of auditory system have been ascertained, however, the influence on CAP adaptation remains unknown. Spoor *et al.* [14] suggested the responsible site of CAP adaptation process is located at the level of

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synapse. Since salicylate and quinine is known to alter the ion channel activity and ion channel activity is closely related to the action of synapse, CAP adaptation process is assumed to be changed by administration of salicylate or quinine. In this paper we examine the effect of salicylate and quinine on the cochlear adaptation using CAP. Changes in CAP adaptation process was supposed to closely relate to the existence of tinnitus when consideration is given to the possible sensation of tinnitus felt by animals after drug administration.

Materials and methods

Animal preparation

Adult male Hartley guinea pigs received an intraperitoneal injection of 25 mg/kg of sodium pentobarbital (32.5–65 mg/ml). Six guinea pigs were allotted for salicylate and five were for quinine experiment. After 15 minutes, animals were tracheostomised for artificial respiration. Following head shaving, Xylocaine® (mixture of lidocaine hydrochloride and epinephrine, 10 mg/ml) was injected subcutaneously and rubbed in gently, then retroauricular skin incision was made to expose a round window. The left carotid artery and left jugular vein were cannulated to monitor systemic blood pressure and to compensate for the serum volume loss, respectively. The temperature of guinea pig was generally maintained at 37 ± 1 °C with a thermostatically controlled blanket (BWT-100, Bio Research Ltd, Nagoya, Japan). A dose of 200 mg/kg of sodium salicylate was administered intravenously, while a dose of 200 mg/kg of quinine hydrochloride was injected intra-muscularly. At the end of the experiment animals were sacrificed with an overdose of sodium pentobarbital.

Acoustic stimulus presentation

Sound stimuli were presented from a loudspeaker (JBL-2450H) placed with its center at 40 cm in front of the guinea pig's head and perpendicular to the animal's auditory meatus. Calibration and monitoring of the sound pressure and tonal waveforms was done by a condenser microphone (NA-41, Rion Ltd, Tokyo, Japan) above the animal's head.

CAP audiograms were determined by short tone-bursts of 2, 4, 8, and 16 kHz. Click-trains have the run from 64 ms to 96 ms and inter-train interval was 500 ms. Both stimuli were generated by masking generator (DPS-727, Dia Medical System Co, Ltd, Tokyo, Japan) and stimulator (DPS-1100D, Dia Medical System Co, Ltd, Tokyo, Japan). The inter-click interval (Δt) was changed from 8 ms to 64 ms (8, 16, 32, 64 ms). The click number was changed from 2 to 10 according to Δt because of the limit of a recording window. Ten clicks were included when Δt was 8 ms, 7 clicks for 16 ms, 4 clicks for 32 ms, and 2 clicks for 64 ms, respectively. The individual clicks were led by 0.1 ms rectangular electric pulses.

The recording sequence was composed of two parts, using a stimulus of short tone-bursts and click-trains with different Δt . After collecting pre-administration data as a control, the same experimental manoeuvre were performed up to over seven hours after administration without changing the electrode positions.

Recording

A silver ball electrode was placed on the round window membrane. Electrical responses were amplified by 10^4 by a biophysical amplifier (AVB-11, Nihon Kohden Ltd, Tokyo, Japan), bandpass filter of which was set at a frequency from 0.08 Hz to 10 kHz, and then fed to computer to be averaged by a MacLab system (AD Instruments Pty Ltd, NSW, Australia) for Macintosh. The activity was sampled 20 kHz for 100 ms after stimulus onset.

Data analysis

Thresholds were determined for every short tone-bursts stimulus. The response to the click-train stimulus was analysed as for the amplitude and half peak width of CAP waveform.

Figure 1 illustrates the method to evaluate CAP amplitudes and half peak width. CAP amplitude is measured from the onset to the peak of CAP. The half-peak width is measured at an amplitude level 50% down from the peak of CAPs. We were able to continue recording before and after drug application for over seven hours (167.8 ± 114.3 min.) in eleven guinea pigs. Guinea pig number 36 was used only to record a response waveform to click trains. Consequently four guinea pigs were applied for

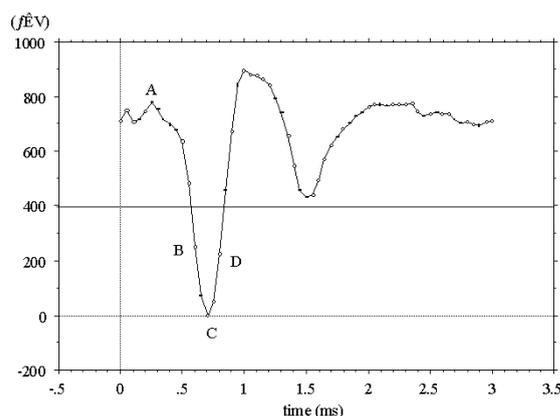


Figure 1 A response waveform and the methods for measurement are shown. The first 3 ms response after onset of click train stimulus is plotted in this figure. Δt is 32 ms and stimulus intensity is 100 dB p.e.SPL. Each circle depicts sampling point. CAP amplitude is measured from the onset of CAP (minimum point: A) to the N_1 peak (maximum point: C). The horizontal line around 400 μ V indicates the half peak. The half-peak width is measured a duration from the first point under the half peak (B) to the last point under the half peak (D) in the CAP response waveform. The half peak width is 0.2 ms in this waveform.

evaluation of the threshold for quinine. Statistical tests for the data obtained before and after administrations were mostly based on the Wilcoxon signed rank test. The comparisons with the control state was made between 18 min. and 60 min. (40.3 ± 3.8 min.) after salicylate administration for and 10 min. and 75 min. (43.6 ± 14.9 min.) after quinine administration. Changes at the $p < 0.05$ level were considered significant. All statistical tests were performed using the STATVIEW 5.0J package for power Macintosh.

Results

Thresholds

CAP thresholds showed 5–30 dB increases from about a half-hour after both salicylate and quinine application and some animals showed a recovery of thresholds during our recording session. Figure 2 depicts the threshold changes to tone bursts of four frequencies after application of drugs. Both drugs induce a mean threshold elevation over 10 dB. Thresholds were elevated with increase in tone-bursts frequencies especially after application of quinine. However, statistical tests showed no significant difference between stimulus frequencies for salicylate. No statistical test was performed for quinine because of the small number ($n = 4$).

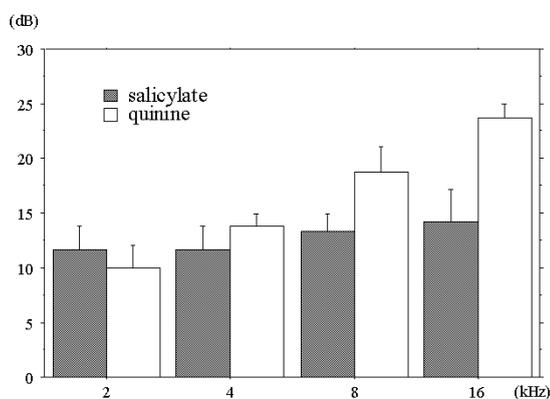


Figure 2 Thresholds of CAP in response to the short tone bursts are shown in this figure. Those for salicylate and quinine are separately illustrated. Stimulus frequencies are 2, 4, 8 and 16 kHz.

CAP adaptation process

The CAP adaptation process was analysed by means of two different indices, which were CAP amplitude and half peak width.

CAP amplitude: Figure 3 depicts the CAP waveform in response to the click train stimulus before and after salicylate administration in representative animal. The Δt is 16 ms and stimulus intensity is 100 dB. Figure 4 illustrates the CAP adaptation process for the same click-train using normalized value of amplitude relative to that to the first click. Additional two stimulus intensities were plotted on the

same figure. The reduction of CAP amplitude was declined after salicylate administration. The same tendency was observed both in other animals and other Δt .

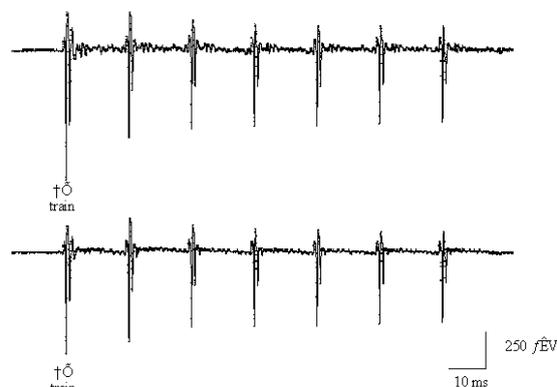


Figure 3 Response waveforms to trains of click are shown in this figure. Upper section illustrates CAP response by pre-salicylate administration and lower section reveals by post-salicylate administration. The Δt is 16 ms and stimulus intensity is 100 dB.

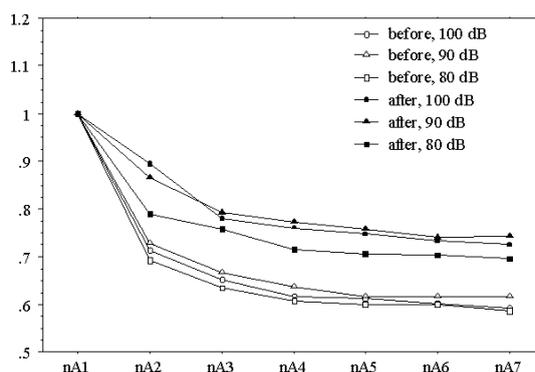


Figure 4 The CAP adaptation process for the same click-train as Figure 3 using normalized value of amplitude relative to that to the first click is illustrated. nA1, nA2, . . . , nA7 represents normalized value of CAP amplitude in response to the 1st, 2nd, . . . , 7th (last) click in the click train, respectively. Additional two stimulus intensities are plotted on the same figure.

Figure 5 depicts the CAP waveform in response to the click train stimulus before and after quinine administration in representative animal. The Δt is 16 ms and stimulus intensity is 100 dB. Figure 6 illustrates the CAP adaptation process for the same click-train using normalized value of amplitude relative to that to the first click. Additional two stimulus intensities were plotted on the same figure. Each CAP is gradually decreased following click numbers before quinine administration. In contrast, after quinine administration, CAP to the second click is distinctly increased and gradually decreased afterward. The same tendency was observed both in other animals and other Δt .

Taking the threshold elevation into account for both salicylate and quinine, we compared the adap-

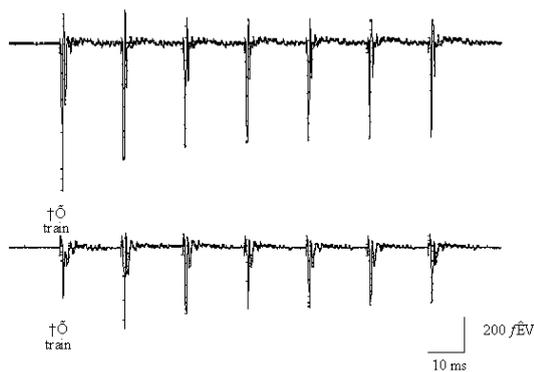


Figure 5 Response waveforms are similarly shown in this figure. Upper section illustrates CAP by pre-quinine administration and lower section by post-quinine administration. The Δt is 16 ms and stimulus intensity is 100 dB.

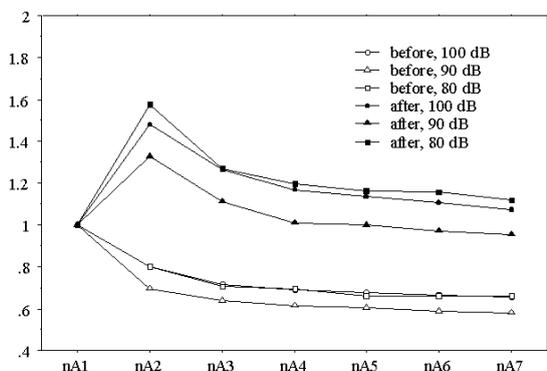


Figure 6 The CAP adaptation process for the same click-train as Figure 5 using normalized value of amplitude relative to that to the first click is illustrated. The layout of the figure is the same as Figure 4. Additional two stimulus intensities are plotted on the same figure.

tation process at adjusted intensities, e.g. if the threshold was elevated by 10 dB, the adaptation process after administration was evaluated at an intensity of 100 dB when compared with that before administration at 90 dB. Even after adjustment, there is still increase in normalized value of CAP amplitude to second click after administration in all guinea pigs.

Half peak width: Figure 7 shows the changes of the half peak width after salicylate administration. The Δt is 16 ms. Changes in widths after application of salicylate are somewhat obscure. Almost the same pattern was observed at the other Δt .

Figure 8 shows the changes of the half peak width after quinine administration. The Δt is 16 ms. Widths are increased after quinine administration. This post-administration change as compared to pre-administration is statistically significant ($p < 0.05$). Interestingly, the widths of post-administration are decreased for the second click in the train stimulus and increased afterward; this is even more obvious when observing the overall

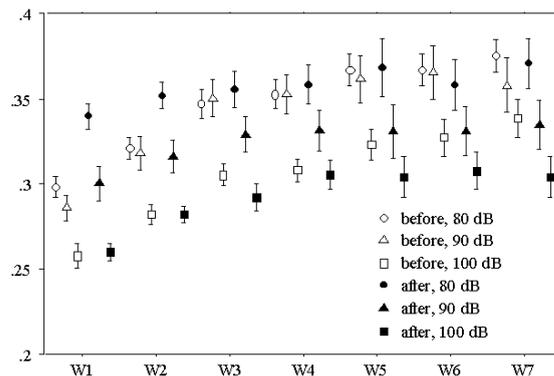


Figure 7 Changes of the half peak width after salicylate administration are shown in this figure. W1, W2, . . . , W7 reveals width of CAP amplitude in response to the 1st, 2nd, . . . , 7th (last) click in the click train, respectively. The Δt is 16 ms and 3 different stimulus intensities are illustrated. Means \pm 1 standard errors ($n = 6$) are indicated.

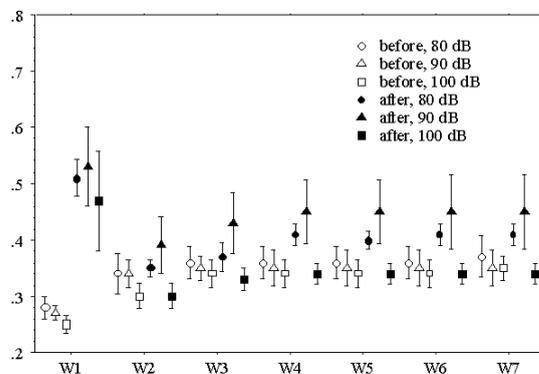


Figure 8 Changes of the half peak width after quinine administration are shown in this figure. The layout of the figure is the same as Figure 7. The Δt is 16 ms. Means \pm 1 standard errors ($n = 5$) are indicated.

shape of the waveform rather than in just looking at the numerical change for the half-peak width (Figure 5). Almost the same pattern was observed at the other Δt .

Discussion

Both salicylate and quinine is known to induce reversible hearing loss and tinnitus in humans. In animal study, we previously showed that thresholds at CF increased by 20 to 30 dB about 2 hours after application of sodium-salicylate and showed no recovery in cat primary auditory cortex [5]. In addition, quinine caused the threshold elevation between 10 dB and 40 dB a half-hour after the application of quinine hydrochloride and some animals showed a recovery of threshold during experimental session [6]. Furthermore, we also observed changes in tuning properties of cortical cells that the tip of the tuning was shifted toward lower frequencies especially after quinine administration. This suggested that the threshold

elevation at higher frequencies somewhat larger than those at lower frequencies. It is compatible with our CAP results in the present study.

CAP amplitude reduction became less dominant after both salicylate and quinine administration. The site where the adaptation occurs remains obscure. Cochlear receptor cell plays no role in the adaptation phenomenon because Russel and Sellick [15] reported that mammalian inner hair cells do not display adaptation when recorded intracellularly. Chimento and Schreiner [16] suggested following three sites for the development of adaptation process. The presynaptic release of neurotransmitter from hair cell, the postsynaptic activation of spiral ganglion dendrites, the transmission along the axon, or a combination of these three sites. The regulation of ion conductances, especially Ca^{2+} conductance might be closely related to the above mentioned three sites. The changes in Ca^{2+} conductances are supposed to induce changes in CAP adaptation process. Dieler *et al.* [2] speculated that the observed swelling of outer hair cells after salicylate application could be mediated by changes in the intracellular calcium concentration. In addition, it was reported that a salicylate application increases the red cell permeability for Ca^{2+} (and Mg^{2+}) and that it activates the Ca^{2+} -sensitive K^+ channel [17]. Besides, quinine was reported to block the Ca^{2+} activated K^+ currents in the red blood cell [18], pancreatic γ cell [19] and in the GH3 cell [20]. It was suggested that quinine act partly by increasing the intracellular availability of a Ca^{2+} [21]. Eleno *et al.* [22] observed increased ^{45}Ca uptake by quinine in isolated mast cells and suggested that quinine opens certain calcium channels and lead to elevate intracellular Ca^{2+} levels. In addition, Ohmori [23] observed that the decay of the inward current carried by Ca and Sr ions was eliminated when 100 microM-quinine was added to the bathing medium and suggested it was probably due to the activation of some Ca-activated K conductance. Both drugs seem to induce the changes in Ca^{2+} channel at hair cell level, which might cause abnormal changes in CAP adaptation process.

There are interesting reports suggesting the relationship between ototoxic effect of salicylate or quinine and Ca^{2+} channel. The tinnitus induced by salicylate or quinine was totally abolished by Nimodipine, an L-type Ca-channel blocker, according to behavioral studies in [24,25]. Zinc was also reported to prevent salicylate-induced hearing impairment [26]. These results suggest that ototoxicity of salicylate is related to Ca^{2+} conductance.

Interesting CAP finding in the present study was observed in changes in the width of CAP waveform. The width was markedly broadened after quinine application while no change was observed after salicylate application. This phenomenon might occur due to the difference between two drug's effect to Ca^{2+} -activated K^+ channel. Salicylate activates the Ca^{2+} -sensitive K^+ [17] whereas quinine block the Ca^{2+} activated K^+ currents in the red blood cell [18], pancreatic cell [19] and in the GH3 cell [20].

It was suggested that the inactivation properties of the potassium current appear to provide a direct explanation for the cumulative broadening of APs [27]. A cumulative potassium current inactivation is supposed to result in a gradual broadening of CAPs in repetitive stimulation. The half peak width of the first click CAP in the click train stimulus was widened after quinine administration, for which quinine as a K^+ channel blocker may be responsible. However, after the second click response, the adaptation process including both reduction of amplitude and broadening of CAP was returned to the same pattern as in pre-administration. This suggests that the K^+ channel was reset or recovered to normal state after the second click in the train response.

Conclusion

Salicylate and quinine induced a CAP threshold elevation and changes in CAP adaptation process. It is suggested that the changes in Ca^{2+} conductance that might result in the suppression of CAP adaptation may contribute to the development of tinnitus. It was also suggested that the effect of both drugs on CAP adaptation were not totally the same because a different change in CAP width was demonstrated between two drug application.

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A comparison of two experimental tinnitogenic agents: The effect of salicylate and quinine on activity of cochlear nerve fibres in the guinea pig

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One of the important physiological correlates of peripherally generated tinnitus is considered to be reflected in increases of spontaneous activity of cochlear nerve fibres [1]. This report compares the effects of two pharmacological tinnitogens, salicylate and quinine, on spontaneous activity measured from single cochlear nerve fibres of the guinea pig. Both salicylate (300–400 mg/kg) and quinine (10–30 mg/kg) were given intravenously. Salicylate was measured in perilymph at levels between 1–2 mM. Quinine could not be detected directly within the perilymph but was likely to be present at levels below the detection limit of 5 μ M. These salicylate levels were associated with changes in the distribution of spontaneous rates (SR) of cochlear nerve fibres. This was primarily seen as a significant increase ($p < 0.01$) in the number of fibres with SRs above 95 spikes s^{-1} , from 13% to 24% post salicylate. In contrast, quinine caused a significant decrease ($p < 0.01$) in the proportion high SR fibres. Employing a separation criteria of 25 spikes s^{-1} for low:high SRs, the ratio changed from 26%:74% in control fibres to 47%:53% in quinine poisoned fibres. These results suggest that perception of tinnitus maybe dependent on *modulation* of SR rather than simply an increase in SR alone

Introduction

Over the last two decades, there has been extensive use of both salicylate and quinine as pharmacological tinnitogens in the development of experimental models of tinnitus [1–9]. The primary reason for this being the consistent reporting of tinnitus, with therapeutic use in man. In the case of salicylate, tinnitus is typically reported when serum levels exceed 300 mg/l or about 2 mM [10,11]. Quinine ototoxicity is also similarly well documented, though the serum levels associated with ototoxicity and tinnitus are considerably lower, falling between 7–20 μ g ml^{-1} or about 20 μ M–55 μ M [10,12,13].

Experimentally, the pharmacological and physiological processes underlying tinnitus point to salicylate acting to affect both inner hair cell (IHC) and outer hair cell (OHC) function [1,6]. Possibly the most important of these being a marked change *in vitro* of OHC electromotility and membrane

conductance characteristics within the therapeutic concentration range [6]. In physiologically well controlled single cochlear nerve fibre studies first carried out by Evans *et al.* [1] it was shown that salicylate not only caused an increase in fibre threshold but also caused a loss of frequency selectivity in these fibres. Most importantly, these studies showed that salicylate was responsible for an *increase* in the spontaneous activity of certain fibres. This increase in spontaneous activity was then considered to represent a physiological correlate of tinnitus at the level of the cochlear nerve. Pharmacologically, quinine would appear to exert its tinnitogenic effect by different modes of action to salicylate [2,7,14,15]. In both human and experimental studies, it has been shown to cause an increase in cochlear threshold but apparently leaves frequency selectivity unaffected [9,13]. Mechanistically, pharmacological studies have focused on the likely role of quinine as both a blocker of a number of different classes of K^+ conductances within the cochlea, and also as a possible Na^+ channel blocker [2,7,14,15].

Up until recently, the effect of quinine at the level of the cochlear nerve fibre *in vivo* had not been

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described [9]. This work, in part presented here, also arose from the Evans lab as part of the effort to further define the physiological correlate of a known tinnitus. In this presentation, the effects of both quinine and salicylate on spontaneous activity in the guinea pig cochlear nerve, are compared and contrasted with respect to the development of objective experimental models of tinnitus.

Methods

Single unit electrophysiological recordings in neuroleptanaesthetised guinea pigs were carried out using 2.7 M KCl microelectrodes. Surgical preparation, monitoring of general physiological condition, data collection and analysis are described in detail elsewhere [16,17]. During single unit recording from the left cochlear nerve, the relevant physiological parameters from each single unit were measured. Spontaneous rates (SR) were measured by averaging electronic counts made over at least a 10 second period in a single fibre. Particular attention was paid to monitoring the animals physiological condition. Body temperature was kept between 37–38°C, and end tidal CO₂ between 4–5%. Where possible, mean arterial blood pressure (MABP) was kept at or above 50 mmHg. If MABP fell below this levels then data were generally excluded as the decrease in MABP may have contributed to deterioration in cochlear function, which could be confounded with ototoxic effect [18,19].

After recording from sufficient numbers of control cochlear nerve fibres, either sodium salicylate (300–400 mg/kg) or quinine hydrochloride (10–30 mg/kg) were slowly administered iv over about 10–20 minutes in normal saline, so as not to cause reduction in MABP. At the end of the single unit recording, microsamples (1–2 µL) of perilymph from the left cochlea, were collected and analysed for salicylate or quinine using fluorimetry [20]. Blood samples were also taken for analysis of plasma levels of drug. Data were analysed using: Students t-test; Mann Whitney U-test, and the chi-squared test.

Results

A total of 178 control fibres were obtained from thirteen animals, and 188 fibres were recorded from eleven animals given salicylate. A total of 38 fibres were recorded from four animals given quinine. Four other animals given quinine had to be excluded from analysis due to the MABP falling below 40 mmHg for the rest of the experiment.

Comparison of salicylate and quinine levels in perilymph and plasma

Penetration of the cochlea by salicylate was rapid, with levels of salicylate above 0.5 mM being detectable in the perilymph within 30 minutes of injection. Mean perilymph concentrations over 2–6

hrs were 1.4 mM ± 0.1 s.e. (n = 9). Mean serum levels were 3.5 mM ± 0.24 s.e. (n = 9). This yields a partition coefficient of about 2.5 between the plasma and perilymph compartments.

In contrast, no quinine in perilymph could be detected 2–4 hours after administration (fluorimetry detection limit 5 µM), whilst serum levels of quinine were 12.5–45 µM. This suggests that the partition coefficient between plasma and perilymph is at least 10:1. This is not dissimilar to the partition coefficient between plasma and CSF in man [12,21]

Comparison of the effects of salicylate and quinine on spontaneous activity

The range of SRs in guinea pig cochlear nerve fibres is typically between 0–130 spikes s⁻¹ [9,18]. The frequency histograms derived from control fibre, as seen in Figure 1(a) is bimodal, with a low SR median of 6 spikes s⁻¹ and a high SR mean of 72 spikes sec⁻¹. The trimodal appearance of that derived from fibres obtained one hour post salicylate in Figure 1(b) is in contrast to this. The first two modes have similar median and mean values to the control, but the third mode has a mean value at about 113 spikes sec⁻¹. This suggests that salicylate is acting to increase the SR of a certain group within the fibre population.

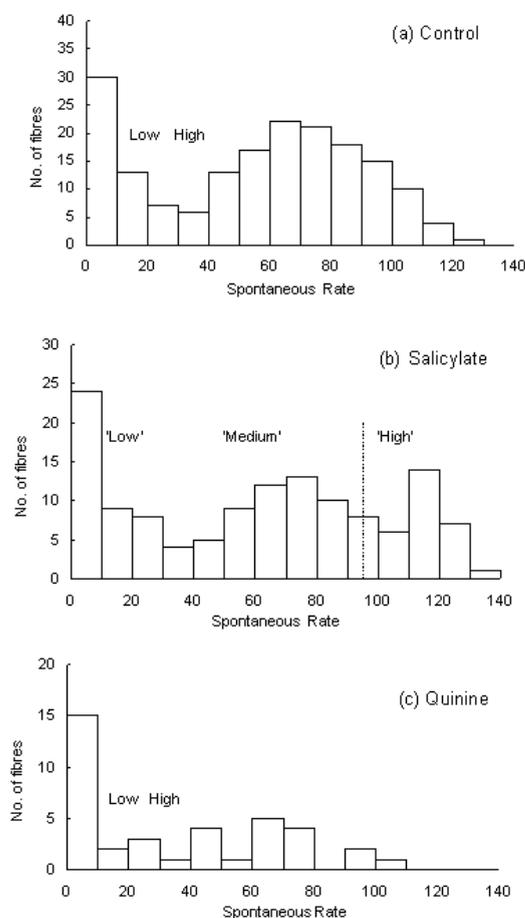


Figure 1 The spontaneous rate frequency histograms obtained from (a) control (b) salicylate and (c) quinine treated fibres.

The relative proportions of fibres in both control and salicylate treated fibres occurring with respect to the trimodal groups seen with the salicylate poisoned fibres are given in Table 1. Here, fibres are further divided into 'low' 'medium' and 'high' SR with these categories now based on the appearance of the post salicylate trimodal histogram. The separation criteria of the three groups being 25 spikes s^{-1} and 95 spikes s^{-1} respectively. Compared to the control population of fibres, the increase in the number of fibres with SRs above 95 spikes s^{-1} from 13% to 24% was found to be significant at $p < 0.01$.

Moreover, the table also indicates that the fibres with increased SR were most likely drawn from a sub-population of fibres with pre-salicylate SRs between 25–94 spikes s^{-1} . In both pre and post salicylate treated fibres, the proportion of 'low' SR fibres remains similar, making up 26% and 27 % of the fibre populations respectively. In contrast, there is a reduction in the proportion of fibres in the 'medium' category from 64% to 49% following salicylate administration. This would suggest that the processes in the IHC driving SRs above about 25 spikes s^{-1} are particularly sensitive to the effects of salicylate. Fibre threshold has been previously shown to be related with SR, with fibres having the more sensitive thresholds being associated with SRs above about 18–20 spikes s^{-1} [22]. From the results described here, this would also suggest that these fibres with the most sensitive thresholds would have a primary involvement in transmission of the salicylate induced tinnitus signal.

Figure 1(c) shows the effect of quinine on the 38 fibres recorded from four animals. Notwithstanding this relatively small number of fibres, the appearance of this frequency histogram is bimodal, with the boundary criterion of 25 spikes s^{-1} being used to define low and high SR fibres. The median values of the low SR fibres was not significantly affected by quinine at $p < 0.2$. In the high SR group, there was a decrease in mean SR from 72 spikes $s^{-1} \pm 2$ s.e. ($n = 131$) to 62 spikes $s^{-1} \pm 5$ s.e. ($n = 131$), which was not significant at $p = 0.07$. This marginal p value is evidence of an effect of quinine on SR, which is more clearly seen when the effect of quinine on the proportions of low: high SR fibres is considered as shown in Table 1. The low:high SR ratio changed from 26%:74% to 47%:53% and this change was significant at $p < 0.01$. This would suggest that quinine is acting to cause a nett downward shift in the spontaneous activity in fibres with a previously high SR.

Table 1 The frequencies of fibres occurring in each of the three nominal SR groups, for control and salicylate treated fibres, with percentage occurrence in the bottom row.

| SR Group (spikes s^{-1}) | Control | One hour post-salicylate |
|--------------------------------|----------|-----------------------------|
| 'Low' (0–24) | 47 | 35 |
| 'Medium' (25–94) | 106 | 64 |
| 'High' (95–140) | 23 | 31 |
| % Low: Med: High | 26:61:13 | 27:49:24 |

Table 2 The frequencies of fibres occurring in the low and high SR groups, for control and quinine treated fibres, with percentage occurrence also given.

| SR Group (spikes s^{-1}) | Control | Quinine treated |
|--------------------------------|---------|-----------------|
| Low (0–24) | 47 | 18 |
| High (25–130) | 129 | 20 |
| % Low: Med : | 26.74 | 47.53 |

Discussion

These results show that salicylate rapidly enters the cochlea to produce a tinnitogenic effects at concentrations of about 1–2 mM. Quinine could not be detected at concentrations above $\mu 5M$, and this indicates that its tinnitogenic activity would be associated with perilymph concentrations below this [9]. The levels reported here for perilymph levels of salicylate are in line with those reported previously to be associated with behavioural indices of tinnitus in the rat [3]. There appears to be no published pharmacokinetic data on the distribution of systemically administered quinine into cochlear compartments, especially with regards to levels likely to be associated with tinnitus. The data presented here about entry of quinine into the cochlea are in no way definitive. They are however in agreement with the minimal levels utilised in cochlear perfusion studies to ascertain the minimal concentrations of perfused quinine that result in measurable ototoxic effect [2], ie between 1–10 μM . They therefore arguably serve as some indication, when appropriate consideration of pharmacokinetics are taken into account [12,21] as to what dosages may be most pertinent to employ, in developing a physiologically relevant model of tinnitus. These levels are also somewhat lower than the mM levels employed in some *in vitro* studies [22].

The most important finding of this comparative report is that the two tinnitogens appear to be having *opposite* effects on spontaneous activity of cochlear nerve fibres. These results suggest that physiologically significant and coherent *modulation* in the SR of the fibre population gives rise to the perception of tinnitus of peripheral origin. At present this remains an interesting possibility that need to be confirmed by other workers, not least because the results obtained for quinine here were from a relatively small sample of fibres. The results presented here also suggest that fibres with SRs above about 25 spikes s^{-1} appear to be most vulnerable to the action of both salicylate and quinine. This is likely to be of relevance in the design of specific tinnitolytic agents which could then be tailored to preferentially exert selective action at these sites.

If peripheral tinnitus was confirmed to arise as a result of some overall modulation of fibre population SR, then it would have potential implications for the development of putative tinnitolytics. Two broad classes of potential tinnitolytics are the Na^+ channel blockers and Ca^{2+} channel blockers. Vari-

ous agents from these two classes have been investigated for their tinnitolytic potential both experimentally and clinically [1,8,24,25]. If these drugs do have effective target sites in the cochlea, then the expectation would be that both these drugs would effect some reduction in the level of cochlear nerve activity [26]. This may be appropriate where a 'salicylate' like increase in SR is responsible for the generation of tinnitus. However, their use is likely to be inappropriate if a 'quinine' like decrease in SR is primarily responsible for the perception of tinnitus. In this case they may even act to depress high SR activity even further.

This possibility should serve as a further general caveat to the interpretation of the results obtained with these or other putative tinnitolytics for the treatment of tinnitus. This is particularly the case when the patterns of cochlear nerve fibre activity likely to underlie peripheral tinnitus require more comprehensive experimental characterisation.

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Somatic modulation appears to be a fundamental attribute of tinnitus

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It is well known that an occasional patient can change her/his tinnitus with a head or neck maneuver. However, it is unknown how widespread this attribute of tinnitus is. This study was undertaken to answer this question. We physically examined 70 consecutive patients seen in our tinnitus clinic for their ability to modify their tinnitus with 16 brief but forceful extremity or head and neck isometric contractions. Regardless of etiology or audiometry, more than two-thirds of all subjects could modulate the loudness of their tinnitus with one or more of these maneuvers. As compared to extremity manipulations, head and neck manipulations were about twice as likely to modulate tinnitus, never were weaker in their effect, and always produced the same type of changes (i.e. louder or softer). These maneuvers sometimes resulted in prolonged effects and could alter pitch as well as laterality of the tinnitus percept. Decreased tinnitus loudness was far more likely to occur for subjects with monaural tinnitus than binaural tinnitus. These results suggest that somatic modulation may be a fundamental attribute of tinnitus on a par with the auditory and affective attributes of tinnitus.

Introduction

Tinnitus remains a puzzling symptom. Many fundamental questions regarding tinnitus are still enigmatic, such as (1) why some patients develop tinnitus and others do not despite an otherwise identical hearing disorder, (2) what determines when patients with a chronic progressive hearing loss develop tinnitus, or (3) why patients with symmetric hearing can develop tinnitus in only one ear. We have recently suggested that a somatic component of tinnitus mediated by auditory-somatic interactions within the brainstem may explain many of these mismatches between hearing loss and tinnitus [1]. At present, however, little is known about this putative somatic component of tinnitus.

Numerous reports have detailed the acoustic (e.g. pitch, loudness, masking properties, duration, or lateralization) and affective properties (e.g. emotional distress, sleep disturbance, distracting effect) of tinnitus; the somatic properties, however, have received much less attention. It has long been known, almost as a curiosity, that some people can modulate their tinnitus somatically. Møller *et al.* (1992) suggested that “some forms of tinnitus may

involve the extralemniscal auditory pathway” and showed that median nerve stimulation could modulate tinnitus in close to 40% of subjects (15% louder, and 23% quieter) [2]. Rubinstein *et al.* (1993) found that about a third of their subjects could influence their tinnitus with jaw movements or pressure on the temporomandibular joint [3]. However there have been no reports in which patients were systematically examined for somatic modulation of tinnitus.

In this report we (a) describe our initial findings from systematic physical examinations of patients for somatic modulation of their tinnitus and (b) interpret these results in terms of the role of somatic-auditory interactions in tinnitus. Our results support the view that somatic modulation is more than a curiosity, and may be a fundamental component of tinnitus on a par with the auditory and affective components.

Methods

Seventy patients (21 F, 49 M; ages 18 to 87) seen consecutively at the Tinnitus Clinic of the Massachusetts Eye and Ear Infirmary between February and August 1999 were first interviewed and then examined for somatic modulation of tinnitus. First each patient was specifically asked whether pushing on the head, turning the head or eyes, clenching the teeth, or anything else could

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change her/his tinnitus. The patient also rated the loudness of her/his tinnitus on a zero to ten scale. Then, while sitting, different forceful contractions were performed by the patient; with each, the patient rated her/his tinnitus loudness and described any change in pitch or lateralization. Nine head and neck contractions were performed by the first 45 patients and an additional seven extremity contractions were performed by the last 25 patients (9 F, 16 M).

Contractions were made for a few seconds – just enough time for the patient to judge their tinnitus. For the head and neck the contractions were as follows: (1) clenching the teeth forcefully; with the head in the neutral position, maximally resisting pressure applied by the examiner to the (2) occiput, (3) forehead, (4) vertex, (5) mandible (upward), (6) right temple and (7) left temple; (8) with the head turned to the right maximally resisting torsional force on the right zygoma; and (9) as in (8), except on the left. The extremity contractions involved (10) locking the fingers of the two hands together and pulling as hard as possible, or resisting maximal pressure to (11) right shoulder abduction, (12) left shoulder abduction, (13) right hip flexion, (14) left hip flexion, (15) abduction or (16) adduction of both hips.

Results

Sixty-eight percent of all subjects could modulate their tinnitus with at least one of the 16 maneuvers. However, prior to the examination, most patients were unaware that any somatic maneuver could effect their tinnitus. Only sixteen of the seventy patients initially reported that they could somatically modulate their tinnitus. The tinnitus of all but one of these subjects could be modulated on physical examination. No subjects were initially aware of any tinnitus modulation with trunk or extremity contraction.

The various maneuvers most commonly produced changes in tinnitus loudness. With head and neck manipulations, 41% of subjects could only increase their tinnitus, 17% could only decrease tinnitus loudness and ten percent could either increase or decrease tinnitus loudness depending upon the maneuver (Table 1). With extremity manipulations, nine subjects could increase their tinnitus loudness, only one could decrease it, and no subject could both increase and decrease it. Loudness changes produced by head and neck maneuvers were always greater than or equal to those produced by extremity maneuvers. Subjects

who could modulate tinnitus loudness with extremity maneuvers could always modulate loudness with head and neck maneuvers, but the converse was not true. Whenever an extremity maneuver increased or decreased tinnitus loudness, head and neck maneuvers did the same. 19% of subjects could increase tinnitus loudness with head and neck maneuvers but not with extremity maneuvers. 7% could decrease tinnitus loudness with head and neck maneuvers but not with extremity maneuvers.

In general if modulation occurred in subjects with binaural tinnitus, it affected the tinnitus for both ears similarly. However, there were some exceptions. One subject with binaural tinnitus reported that pressure applied to the occiput, forehead, or right temple increased tinnitus loudness from 5/10 to 8/10, in the right ear only. Another man described that his monaural right tinnitus disappeared with left temple pressure only to have tinnitus emerge in his left ear. A third subject with binaural tinnitus reported that pressure on either temple caused her tinnitus to shift its location toward the opposite ear. A fourth patient described that her tinnitus was in both ears but worse on the right; with pressure on either temple or turning to either side, her tinnitus became slightly louder on the right and softer on the left.

In five patients, changes in tinnitus loudness persisted long after the series of brief maneuvers had been completed. This was most pronounced for two subjects. For one, loudness increased from 5/10 to 10/10 after right temple pressure and remained elevated for about 10 minutes. In another patient, loudness decreased from 10/10 to 3.5/10 and her tinnitus changed from binaural to monaural; tinnitus loudness and location stayed in this altered state for the remainder of the visit.

Maneuvers also produced changes in tinnitus pitch. Twelve patients described such changes. Ten of these twelve reported changes in loudness as well. Of the seven who described the change in pitch as a "simple," six reported an increase in pitch and one described his tinnitus as being "less shrill." Of all sixteen maneuvers, clenching the teeth most commonly affected pitch. As for loudness, changes in pitch were more common for head and neck maneuvers than for extremities maneuvers. Of the 25 subjects tested with extremity maneuvers, six reported pitch changes with head and neck maneuvers while only one reported them for an extremity maneuver.

Of the 25 subjects tested with both head and neck and extremity maneuvers, the number whose tinnitus loudness could be modified with each of the 16 maneuvers is shown in Figure 1. The pattern of

Table 1 Effect of somatic maneuvers involving the extremities (27 subjects) or head and neck (70 subjects) on tinnitus loudness

| | Increase | Decrease | Increase & Decrease | |
|--|----------|----------|---------------------|----------|
| | | | Decrease | None |
| Extremity Modulation (N = 27) | 9 (33%) | 1 (4%) | 0 (0%) | 17 (28%) |
| Head & Neck Modulation (N = 70) | 29 (41%) | 12 (17%) | 7 (10%) | 15 (33%) |

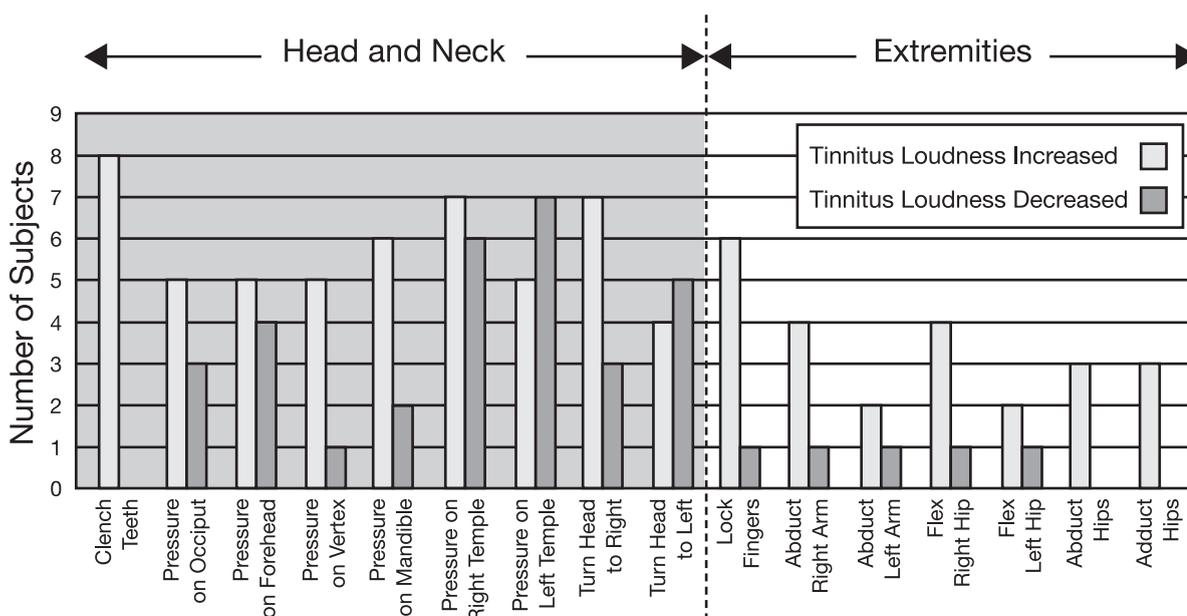


Figure 1 Histogram of the number of patients who reported a change in the loudness of their tinnitus for each of the sixteen somatic maneuvers (x-axis) that formed the basis of the physical examination. Only the patients with both head and neck and extremity maneuvers are included. Of these 25 patients, 17 could modulate their tinnitus loudness with at least one of the maneuvers.

modulation was highly variable. Some subjects could modulate for only one of the sixteen maneuvers, while others could modulate for several of them. Clenching the teeth only increased tinnitus loudness, but every other maneuver could produce either an increase or a decrease depending upon the patient. Similar findings were obtained for the other 45 subjects who had only head and neck testing, except one subject reported her tinnitus decreased with clenching. Of all subjects who were tested with clenching, 28% reported an increase and 1% a decrease in tinnitus loudness.

No relationship between the pattern of somatic modulation and tinnitus etiology or audiometric findings was apparent. The patients who could be modulated carried the following diagnoses: Meniere’s disease, unilateral acoustic neuroma surgery with deafness, noise-induced hearing loss, multiple sclerosis, ototoxicity, head trauma, presbycusis, familial hearing loss or idiopathic. Clearly tinnitus can be modulated in patients with a wide range of etiologies.

There was a striking relationship between decrease in tinnitus loudness and tinnitus laterality. Of the twelve subjects whose tinnitus loudness only decreased with somatic modulation, 67% described their tinnitus as monaural and yet monaural tinnitus subjects only accounted for 36% of all subjects tested (Table 2). Moreover, the four subjects

with the largest decreases in tinnitus loudness (between 6.5/10 and 4/10) all had monaural tinnitus. By the z-test, this difference in the incidence of decreased tinnitus loudness for these two groups is statistically significant at the $p < 0.05$ confidence level.

Discussion and conclusions

Our systematic physical examination of 70 unselected consecutive patients showed that somatic manipulations could alter tinnitus in about two-thirds of all subjects regardless of etiology or audiometry. The fact that such a substantial fraction of the patients seen in our clinic showed somatic modulation suggests that somatic modulation is a more common property of tinnitus than has been previously recognized and as reported in two earlier studies [2,3]. This observation raises other questions. For example we have a patient who normally has no tinnitus but can induce tinnitus with a somatic maneuver of the head. Our findings in this report raise the possibility that, with systematic testing, such phenomena may be found to occur commonly in subjects who do not report having tinnitus. If somatic maneuvers can alter the perception of phantom sounds, another issue is whether they can alter the perception of an externally presented

Table 2 Effects of somatic maneuvers on tinnitus loudness in subjects with monaural (25 subjects) and binaural (45 subjects) tinnitus

| | Increase | Decrease | Increase & Decrease | None |
|-----------------------------------|----------|----------|---------------------|----------|
| Monaural Tinnitus (N = 25) | 8 (32%) | 8 (32%) | 2 (8%) | 7 (28%) |
| Binaural Tinnitus (N = 45) | 21 (47%) | 4 (9%) | 5 (11%) | 15 (33%) |

sound as has been reported for electrical stimulation of the median nerve [2].

While more than two-thirds of all patients could somatically modulate their tinnitus, nearly one-third could not. One possible reason for the lack of modulation is that the appropriate muscles were not activated by the maneuvers used, but might have been with other maneuvers. Consider, for example, the fact that two patients could only be modulated by one of the 16 maneuvers. If that one maneuver had not been performed these two patients would have been considered as non-responders. Another possibility is that, in some subjects, certain somatic maneuvers activate muscle groups that increase tinnitus loudness and others that decrease tinnitus loudness, so that the net result is no modulation of tinnitus. A third possibility is that some forms of tinnitus may simply lack a "somatic component." If so, then somatic modulation would provide a basis for distinguishing subpopulations of tinnitus subjects just as acoustic properties (pitch, loudness, masking properties, or lateralization) have been used to classify subpopulations of tinnitus patients [4,5].

The lesser effectiveness of extremity manipulations as compared to head and neck manipulations suggests that inputs to the auditory pathway from the cranial nerves and upper cervical region of the spinal cord play a greater role in the somatic modulation of tinnitus than inputs from the more caudal

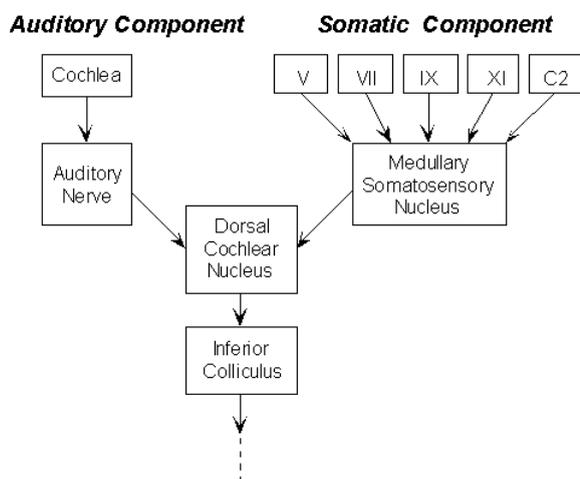


Figure 2 Schematic diagram of somatic-auditory interactions at the level of the dorsal cochlear nucleus. The dorsal cochlear nucleus receives ipsilateral auditory and somatic inputs (via the medullary somatosensory nucleus [6]). Our hypothesis is that the interaction between these two classes of inputs (a) determines whether or not tinnitus develops and (b) accounts for somatic modulation of tinnitus. A decrease in the somatic or auditory input to the dorsal cochlear nucleus is disinhibiting [7] and results in increased dorsal cochlear nucleus output to the inferior colliculus and higher centers, which ultimately leads to phantom sound perception (tinnitus). Presumably such tinnitus would be monaural because it arises from one cochlear nucleus. Roman numerals refer to the cranial nerves that are known to converge on the medullary somatosensory nucleus [8]. C2 refers to the second cervical dorsal root.

spinal cord. It is even conceivable that the influence of the extremities is artifactually high in our data, as would be the case if the extremity effects were not due to the extremity muscle contractions per se, but were instead a consequence of accessory contractions of head and neck muscles. Reasons for this suspicion are that (a) many subjects showed modulation only with manipulation of the head and neck, (b) no subject showed modulation with extremity manipulation without also showing modulation with head and neck manipulation, and (c) extremity modulation always produced the same type of loudness modulation (i.e. louder or softer) as head and neck modulation. Thus, it is possible that lower regions of the spinal cord actually play little or no role in the somatic modulation of tinnitus.

The greater involvement of upper rather than lower spinal cord regions in somatic modulation fits with our previous observations concerning somatic insults and tinnitus. We noted a correlation in some patients between the onset of tinnitus and such somatic insults as a dental abscess, or an upper cervical nerve root block – insults that specifically involve the head and upper neck and, thereby, the cranial nerves and upper cervical spinal cord [1]. These observations, combined with those of the present study, suggest that the neural circuitry mediating the onset of tinnitus after a somatic injury may also subserve somatic modulation of tinnitus.

Our finding that monaural tinnitus patients were far more likely to show a decrease in tinnitus loudness with somatic modulation than were binaural tinnitus patients is interesting in light of our recent proposal concerning the neural circuitry that may underlie the somatic component of monaural tinnitus [1]. We specifically suggested a neurological pathway that could account for a group of normal hearing patients with monaural tinnitus closely coupled to a somatic event. We proposed that, through a (known) multisynaptic pathway, head and neck somatic inputs ultimately disinhibit the output of the ipsilateral dorsal cochlear nucleus, resulting in tinnitus (Figure 2). We speculate that decreases in loudness in response to somatic maneuvers in patients with monaural tinnitus may occur because (1) the somatic pathway to the dorsal cochlear nucleus is activated, (2) inhibition of the dorsal cochlear nucleus is restored, and, consequently, (3) tinnitus loudness decreases.

A somatic component to tinnitus may provide the "missing link" needed to explain many unresolved issues in the tinnitus field. For example, it may account for the occurrence of tinnitus in instances where there is no auditory insult [1]. Likewise, it may explain why some patients develop tinnitus and others do not despite an otherwise identical hearing disorder. Somatic modulation may also account for reports of controlling tinnitus with physical methods such as acupuncture, manipulation, or scalp electrical stimulation [9–11]. The patients who respond to these therapies may be those (a) whose tinnitus loudness decreases with somatic

maneuvers and (b) in whom a brief maneuver can result in a prolonged effect.

We conclude that, rather than being an oddity, somatic modulation may be a fundamental property of tinnitus which can provide insights into understanding some of the basic mechanisms of tinnitus, can be the basis for distinguishing subpopulations of tinnitus subjects, and may be the basis for past successes in treating tinnitus. If this tinnitus factor can be better understood, it may be possible to use it as a treatment for tinnitus on a large scale.

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An animal model of noise-induced tinnitus

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Cochlear, hearing loss-related tinnitus is the most common type of tinnitus observed in clinical practice, but the link between these two phenomena is not straightforward. For example, some patients with no apparent hearing loss experience tinnitus, while other patients with profound hearing loss do not experience tinnitus. We proposed a discordant damage hypothesis which explains why hearing loss and tinnitus, while linked, are not related in a cause-effect manner (Jastreboff PJ. Phantom auditory perception (Tinnitus): mechanisms of generation and perception. *Neuroscience Research* 8: 221–254, 1990; Jastreboff PJ. Tinnitus as a phantom perception: Theories and clinical implications. In: *Mechanisms of Tinnitus*, eds. J Vernon, A Moller. Allyn & Bacon, Massachusetts, Chapter 8, pp. 73–87, 1995).

To study this most clinically relevant type of tinnitus and to assess a discordant damage hypothesis experimentally, it was necessary to create an animal model of cochlear tinnitus and evaluate both hearing loss and tinnitus in the same animal, as well as to separate effects which could be related to tinnitus from those resulting from hearing loss. The modification of our animal model of tinnitus induced by administering either salicylate or quinine, allowed for creation of an animal model of hearing loss-related tinnitus.

The model presented here involves exposing animals to high intensity sound, thereby causing hearing loss and presumably tinnitus. The peripheral damage to the cochlea is evaluated by frequency-specific ABR and distortion product otoacoustic emission (DPOAE) measurements. The behavioral manifestation of tinnitus was evaluated using a method that has been validated by our work with pharmacologically-induced tinnitus. Furthermore, a method is presented that statistically assesses whether tinnitus is present and, if so, its extent in individual rats, therefore allowing us to directly address the relation of hearing loss, damage of the outer hair cell system and tinnitus in the same animal.

Rats were trained under three experimental situations: (1) unilateral exposure via the closed system to exposure for 20 min of 110 dB SPL, 7.8 kHz pure tone performed under Nembutal anesthesia; (2) unilateral removal of the tympanic membrane performed under Nembutal anesthesia; and (3) anesthesia only. Animals from each experimental situation were divided into two groups: One with the treatment performed before, and the other after, suppression training. The difference between the before and after groups has been shown to provide an assessment of the behavioral manifestation of tinnitus.

The extent of tinnitus in individual rats was assessed by using the area difference for the period of extinction between the average of data from the Before or Control group and the individual rats from the After group. On the basis of the variability within the Before or Control group, the probability of the given value of the area difference from the After group can be calculated using the z-test.

The results can be summarized as follows:

- (1) Statistically significant behavioral manifestation of tinnitus emerged in groups exposed to the tone, but not in groups with removed tympanic membrane, or in rats with anesthesia alone. This suggests the need of damage to the cochlea for tinnitus emergence.
- (2) Statistical analysis of the behavior of individual rats revealed that 50% of rats exposed to the tone exhibit significant manifestation of tinnitus, while no rat reached the level of significance in the group with tympanic membrane removal;
- (3) Correlations between an analysis of the extent of the behavioral manifestation of tinnitus and of the hearing loss revealed a weak relationship for the group with sound-induced hearing loss ($p < 0.05$), and no significant association for the group with tympanic membrane removal (NS);

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- (4) Hearing loss cannot be used as predictor of the presence of tinnitus since, similar to clinical findings, our data indicate that rats with similar hearing losses exhibit a totally different extent (or presence/absence) of tinnitus, and animals with a similar level of tinnitus may have significantly different hearing losses.

The analyses of the behavioral manifestation of tinnitus with changes in DPOAE, ABR, and the spontaneous single unit activity revealed significant correlations between the behavioral manifestation of tinnitus and specific parameters of DPOAE changes. These results support the discordant damage hypothesis. Finally, the emergence and parameters of the bursting-type single unit spontaneous activity was highly correlated with the behavioral manifestation of tinnitus.

Creating an animal model of tinnitus appears to be a contradiction in terms. Since we are unable to detect tinnitus in humans in an objective way, how are we going to do it in animals when we cannot even ask them any questions regarding their perception or the presence of tinnitus? However, by use of a specific behavioral technique, it seems that this goal can be achieved, and for last 16 years we have been using this model. The basic idea was to condition animals to be afraid of silence and testing of this conditioned fear, while tinnitus external sound was introduced at various stages of the experimental procedures.

Until recently, we used pharmacologically-induced tinnitus by administration of salicylate or quinine. However, cochlear, hearing loss-related tinnitus is the most common type of tinnitus observed in clinical practice [1,2]. The mechanisms of its generation are speculative and the lack of an animal model of hearing-loss related tinnitus has severely limited the possibility of studying its mechanisms.

Another limitation is that until now the results from groups of rats were averaged and the differences between group means were analyzed and evaluated. This approach, necessary during the initial stages in establishing an animal model and finding basic correlates of tinnitus, has two main shortcomings. First, salicylate or quinine induced-tinnitus is extremely rare in clinical practice, where in the majority of cases tinnitus can be related to some peripheral damage to the cochlear, and is frequently related to sound-induced hearing loss. Secondly, once the possibility of detection of tinnitus in animals and basic parameters has been shown, the next stage is to correlate physiological measures (i.e., neuronal and metabolic activities within the brain, biochemical changes, etc.) with the behavioral manifestation of tinnitus. However, except for salicylate, which in high doses seems to induce tinnitus in 100% of the cases, other methods induce tinnitus in only a proportion of the subjects. Human data indicates that after high level sound exposure approximately 50–60% of the subjects experience tinnitus. In the case of tinnitus, when some damage to the cochlear was induced by sound, another issue became critical – separating physiological and behavioral effects resulting in tinnitus from the effect of hearing loss.

Consequently, our aim was to create a model in which it would be possible to induce tinnitus and hearing loss by exposing animals to well-controlled high levels of sounds, while being able to separate and evaluate the hearing loss from tinnitus in the individual animals. This presentation outlines the main points and results of this study.

The main model is based upon training animals with silence as conditioned stimulus and testing extinction of this reflex with and without experimental manipulation aimed at inducing tinnitus [3–10]. Briefly, to create an animal model of tinnitus, it was necessary to develop a paradigm that would allow for detecting tinnitus, the phantom perception of continuous sound of unpredictable quality which cannot be switched on and off at precise moments of time. This precludes the use of typical behavioral conditioning, which relies on the association of a brief conditioned stimulus (CS; e.g., a tone) with a reinforcement (e.g., a footshock) presented at the end of the CS.

The solution was to train animals to fear silence, while associating any type of sound with safety. The fear induced by silence can be measured using a method proposed by Estes and Skinner [11]. Presumably, if we induce tinnitus in rats (e.g., by salicylate administration) even when all external sounds are switched off, the subjects are less afraid, as they will not perceive silence but rather the sound of tinnitus. The decrease in their fear levels should reflect the presence of tinnitus.

This rationale is implemented in the following manner [3]: From the beginning of the procedure, thirsty rats are exposed continuously to mild noise (62 dB SPL) in home and experimental cages. After the initial period of water deprivation and lick training, rats were exposed five times to a 1 minute offset of noise (silence) during a 45 minute experimental session. This acclimation day allowed for assessment of whether the offset of noise alone had any inherent effect on licking rates, perhaps by inducing fear, which could be demonstrated by a reduced rate of licking. The level of fear could be measured by its impact on the subject's drinking, measured as a change in the rate of licking using a suppression ratio defined as $R_B = A/(A + B)$; where B denotes the number of licks during 1 minute of CS, and A denotes the number of licks during 1 minute period of time before the CS [3]. This ratio has been thoroughly discussed in behavioral literature [12,13], so

that an appropriate frame of reference for interpreting data from this model was available. The ratio equals 0.5 when the CS has no influence on the rat's drinking rate, and decreases toward zero when the CS is inducing fear. For the acclimation day, the expectation was that since the offset of noise had not been associated previously with any kind of reinforcement, the R_B should be within the range of 0.4–0.6 (Figure 1). During the next 2 days of suppression training, each of the five CS periods (1 minute offsets of noise) was terminated by a single footshock. Since the ambient level of sound was very low, the subject associated the offset of background noise, silence, with an unpleasant stimulus. Rats learned quickly that the silence indicated an incoming shock, and they exhibited fear when the background sound was switched off, which was reflected in the gradually diminishing values of R_B (Figure 1, days T1 and T2). Seven days of extinction followed (E1 to E7), during which rats were presented with five daily offsets of noise, but footshocks were no longer given. As a result of this procedure, the fear of the subjects presumably decreased and the values of R_B gradually returned to the pretraining level of 0.5.

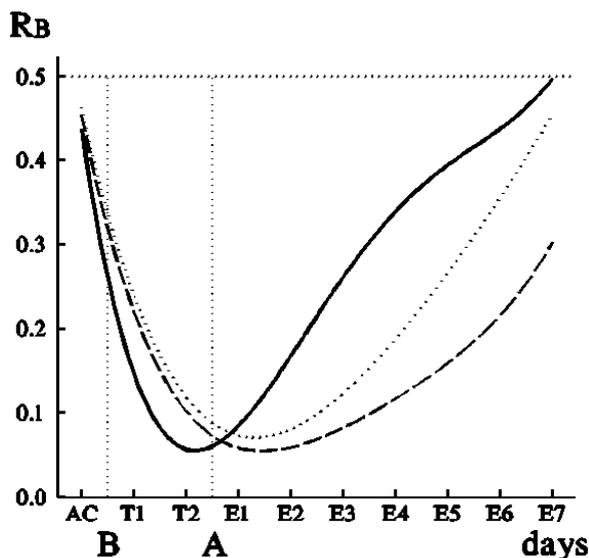


Figure 1 Behavior of animals during testing with salicylate-induced tinnitus. Continuous line – group with daily salicylate administration starting after Pavlovian suppression training; dashed line – salicylate administered starting before suppression training; dotted line – control group with saline administration. All symbols described in text. The average area between curves for days T2 to E7 provides the behavioral manifestation of tinnitus.

Notably, because rats are trained with silence, created by switching off the external background noise, the procedure by definition is not sensitive to the spectrum or the intensity of the tinnitus sound in wide ranges, as any sound would be different from silence. This feature, which was checked by employing tones of different frequencies to mimic tinnitus [6,7], was important, because it indicate

that the paradigm will work without placing significant constraints on the tinnitus sound.

Tinnitus, induced by daily injections of salicylate, was introduced either before or after suppression training (A and B in Figure 1) for the following reasons. When we induced tinnitus in rats after they had acquired a fear of the noise offset (silence), they would still hear something during the noise offset, and the process of extinction of acquired fear would be facilitated. In contrast, if tinnitus was induced before suppression training, then during the training when the background noise was switched off, tinnitus was still perceived and the training would be associated with the tinnitus sound imposed on the silent period with shock (i.e., the tinnitus sound became part of the CS to fear). Since tinnitus was present during all extinction days, the process of extinction would be extended as compared with the control group. Figure 1 shows the fourth order polynomial regression of real data, with 350 mg/kg of sodium salicylate administered s.c. daily with the injections starting before (dashed line), or after (solid line), suppression training together with results from the control group with daily saline injections (dotted line).

Some modification of this basis paradigm was needed for work with sound-induced tinnitus. For behavioral experimentation, it was crucial that the general level of binaural hearing in the rats was not affected significantly. Although we have shown in previous experiments that hearing loss does not affect the detection of tinnitus, from the behavioral point of view it was more convenient to assure that the threshold of hearing of the rats was not changed significantly. This necessitated inducing a unilateral hearing loss, with the other ear providing unchanged hearing. As it was very difficult to expose an awake animal to sound, rats were anesthetized with Nembutal and the sound was supplied in a closed system.

Another issue was to assess if the decrease of the auditory input of a subject by inducing conductive hearing loss but without damaging the cochlear, would induce tinnitus. In a separate group of rats, conductive hearing loss was caused by the removal of the tympanic membrane, and rats were evaluated in the same way as those with sound-induced hearing losses. The final group was composed of animals who were only anesthetized at the same point of training as those with sound-induced hearing losses, before or after 2 days of Pavlovian suppression training.

A total number of 102 rats were studied. As exposure to sound had to be conducted under Nembutal anesthesia, a one day recovery period was needed. Consequently, we ran additional control groups with animals anesthetized but not subjected to any further experimental manipulations before ($n = 5$) and after ($n = 6$) suppression training, and compared the behavior of these two groups. There was no statistical difference between these groups (ANOVA, NS). Thus, the introduction of anesthesia and the day of rest did not influence animal behavior, and there were no differences due to the

fact that these procedures were performed before or after behavioral training.

Notably, when sound-induced injury, which was expected to result in tinnitus in some animals, was introduced before ($n = 14$), or after ($n = 8$) suppression training, the behavior of the rats followed the pattern observed for animals injected with salicylate. That is, the group with cochlear injury introduced after suppression training (Figure 2, triangles) exhibited faster extinction as compared with the group in which exposure to tone was performed before suppression training (Figure 2, squares). This difference is highly significant ($p < 0.01$). However, when results of the groups of animals with conductive hearing loss were introduced before ($n = 7$) and after ($n = 9$) suppression training and compared, there were no differences between these groups.

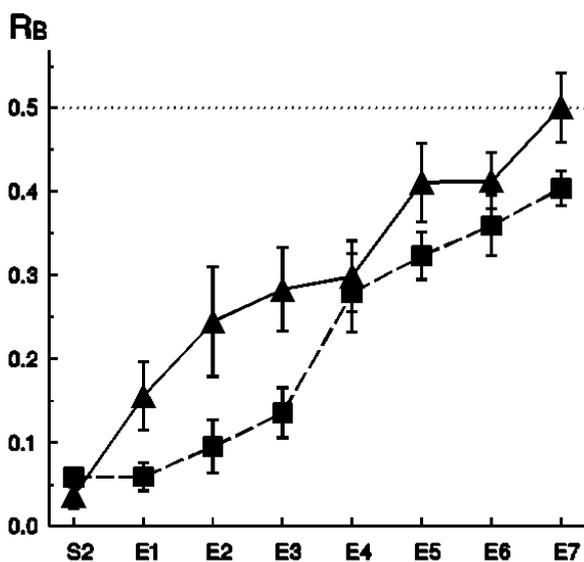


Figure 2 The behavioral manifestation of tinnitus in rats exposed to high level of a pure tone. Note difference between groups of animals exposed to the sound before and after Pavlovian suppression training.

These results are consistent with the postulate that some animals with sound-induced hearing loss experienced tinnitus and thus exhibited the same pattern of behavior (faster extinction in the group with tinnitus induced after suppression training as compared with the group with tinnitus induced before suppression training), which we have reported in tinnitus evoked by salicylate and quinine administrations or when the external sound mimicking tinnitus was introduced at the proper stages of training. Based on clinical reports, we expected that only about 50% of the rats would develop tinnitus and therefore the average effect would be smaller as compared with results from salicylate-induced tinnitus where (both the literature and our data) show that practically 100% of the subjects given sufficiently high doses of salicylate experienced tinnitus.

Of particular significance are results from the groups with conductive hearing loss. As shown

previously [3], our paradigm is not sensitive to hearing loss in general, and even less sensitive to hearing loss induced only in one ear. These data fully support this postulate, as introducing conductive hearing loss on one side did not effect animal behavior. Accordingly, differences in animal behavior with sound-induced versus conductive hearing loss were consistent with the postulate that animals with sound-induced, but not conductive, hearing loss experienced tinnitus. This postulate has been further investigated by analyzing behavioral data from individual animals and correlating the data with the extent of hearing loss in the same animal.

We have developed a method for assessing the extent of tinnitus in individual rats based on using the area difference for the period of extinction between the average of data from the Before group and the individual rats from the After group [5,9,10]. On the basis of the variability within the Before group, a probability of the given value of the area difference from the After group could be calculated using the z-test ([14], pp 166–169). Results of application of this method revealed that while all animals from conductive hearing loss are within the nonsignificant zone, the animals from groups with sound-induced hearing loss exhibited a different pattern, with three rats deeply within the nonsignificant zone, two rats just on the border of significance (one just below and one just above) and three rats well within the significant difference zone. These data are in full agreement with the prediction based upon human data that approximately 50% of the rats will develop tinnitus, with 37.5% of rats well above the borderline of significance.

The issue of the usefulness of hearing loss as a predictor for the presence of tinnitus and whether our behavioral paradigm was affected by hearing loss was explored further by correlating data of the behavioral manifestation of tinnitus with maximal hearing loss measured in the same animal. The data from animals with conductive hearing loss did not reveal significant correlation ($r = 0.266$, NS). Thus, the behavioral manifestation of tinnitus was not dependent on the hearing loss per se. However, in animals with sound-induced hearing loss there was a significant correlation of the behavioral manifestation of tinnitus with the extent of hearing loss ($r = 0.764$, $p < 0.05$).

Notably, the hearing loss itself could not be used as a predictor of the tinnitus presence. Some animals have the same extent of hearing loss with or without tinnitus. This was particularly evident when we compared data from animals with the highest level of hearing loss to groups with conductive versus sound induced hearing losses. While animals with sound induced hearing loss exhibited the behavioral manifestation of tinnitus to various extents, rats with a high level of conductive hearing loss did not exhibit any indication of having tinnitus. Moreover, even in the group with sound-induced hearing loss, there was only a mild correlation between the behavioral manifestation of tinnitus and the hearing loss. The variability of the

extent of hearing loss after exposure of animals to the same sound is consistent with literature [15,16].

The presented results are consistent with the postulate that our paradigm is insensitive to hearing loss, and detects and evaluates the extent of tinnitus disregarding accompanied hearing loss. Our results in sound—exposed animals can be explained by the assumption that both the extent of tinnitus and the hearing loss are related in a roughly proportional manner to the extent of cochlear damage. As such, the correlation of tinnitus and hearing loss is secondary, and while indicating a general trend, this correlation cannot be used for predicting the presence of tinnitus. The detailed analysis of DPOAE reflecting the extent of damage of the OHC system might perhaps provide us with better insight into the mechanisms of sound-induced tinnitus and a better tool for predicting the presence and extent of tinnitus.

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Chemistry in the hamster dorsal cochlear nucleus after loud tone exposure

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There is evidence that exposure to loud tones leads to tinnitus and to increased spontaneous activity in the hamster dorsal cochlear nucleus, but the chemical basis for this change remains unknown. We measured concentrations of amino acids, which include 3 major cochlear nucleus neurotransmitters, and activity of an enzyme of oxidative energy metabolism, in layers of the hamster dorsal cochlear nucleus. Some of the hamsters had been exposed to loud tones, while others were non-exposed controls. Using high performance liquid chromatography, only small differences in concentrations of some amino acids were found between exposed and control animals with either 2-day or one-month survival periods. Using a fluorometric method for malate dehydrogenase activity, no difference was found in any layer between the two dorsal cochlear nuclei of tone-exposed hamsters with one-month survival periods, nor was any difference found between exposed and control animals. Our results suggest that the increased spontaneous activity in the dorsal cochlear nucleus of hamsters previously exposed to loud tones is not related to major changes of amino acid metabolism or oxidative energy metabolism in the tissue.

Introduction

Central tinnitus is a common and potentially severe problem for many adults, especially those with noise-induced hearing loss [1]. There is some information which suggests that central tinnitus may result from increased spontaneous activity of central auditory neurons, in the dorsal cochlear nucleus (DCN), inferior colliculus, and auditory cortex [2–6]. Since the analysis of auditory information in the DCN precedes that in the inferior colliculus, to which it sends a major projection, changes in neural activity in the DCN could account for effects in the colliculus and cortex.

The chemistry of neurons underlies their physiology. Therefore, we have begun a search for chemical changes in the DCN that might accompany its increased spontaneous activity in hamsters after exposure to loud tones. Using high performance liquid chromatography (HPLC), we have measured the concentrations of amino acids, which include the 3 major neurotransmitters of the cochlear

nucleus. The amino acid glutamate may be the neurotransmitter which auditory nerve fibers release to excite cochlear nucleus neurons shortly after sounds activate the cochlea [7,8]. It also serves as an excitatory neurotransmitter for the small interneurons of the cochlear nucleus known as granule cells [9]. The amino acids glycine and aminobutyrate (GABA) are inhibitory neurotransmitters of some cochlear nucleus interneurons and of some pathways to the cochlear nucleus from other parts of the brain, especially higher-level auditory centers such as the superior olive [10–13].

In addition to these 3 amino acids, our HPLC assay provided results for 8 other amino acids not as closely related to neurotransmission, but still important for the structure and metabolism of nerve cells [14–16]: aspartate and glutamine, which are metabolically closely related to glutamate; serine, which is metabolically closely related to glycine; taurine, which may be involved in control of membrane excitability; and threonine, arginine, alanine, and tyrosine.

Besides amino acids, activity of malate dehydrogenase (MDH), an enzyme involved in oxidative energy metabolism, was measured to estimate any effects of the loud tone exposure on this critical component of neuronal metabolism.

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We coordinated our chemical measurements with physiological measurements of DCN spontaneous activity [4], carried out on many of the same hamsters before freezing their brains for chemical analysis. Since the effects of the loud tone exposure vary considerably among hamsters [3], this ensured that the chemical analyses were done on samples from DCNs wherein increased spontaneous activity had been measured. However, since the chemistry could be affected by the experimental procedures necessary for carrying out the physiology, samples were also assayed from DCNs of hamsters upon which physiological recordings were not made. Hamsters were studied at 2 days after loud tone exposure, a time when there is no increase in spontaneous activity in the DCN [17], and at one month after loud tone exposure, when there is a large increase in DCN spontaneous activity [4]. Based on the exposure procedure, we looked for differences between exposed-side and contralateral DCN, since the exposed side should have a larger effect of the loud tone. The contralateral ear should also be affected by the loud tone because of spread of the sound across the head [18], so we compared the results for both sides of exposed hamsters to those for both sides of control hamsters.

Methods

The methods for loud tone exposure, microdissection, assay of amino acid concentrations, and assay of MDH activity have all been published previously [3,19–22].

Anesthetized adult hamsters were exposed to a 125–130 dB 10 kHz tone into the left ear for 4 hours. Control hamsters were similarly anesthetized but not exposed to the loud tone. At certain survival times after the exposure, animals were anesthetized for electrophysiological recording of multiunit spontaneous activity in the DCN [4]. After the recording session, the hamsters were euthanised, and their brains were quickly removed and frozen. Other hamsters were similarly euthanised without any recording session. Frozen brains were sectioned transversely through the cochlear nuclei at 20 micrometers thickness. Alternate frozen sections were loaded into aluminum racks for freeze-drying. Intervening sections were stained with cresyl violet. The DCN portions of freeze-dried sections were microdissected into samples representing the 3 layers: molecular, fusiform soma, and deep, usually at three locations along the medial-lateral axis. Dissections were also done in which samples were cut as slabs oriented perpendicular to and crossing all the layers, to provide a one-dimensional map of chemical distributions along the tonotopic axis of the DCN [4]. Samples were weighed on quartz fiber microbalances and loaded into tubes for chemical assays.

Amino acid concentrations were measured via HPLC [22]. It was discovered that the peak size for glutamine varied over time in a way that we did not fully understand. Thus, comparisons among data for glutamine are limited to those obtained at a

similar time. Data for aspartate were not obtained for some samples because of a problem with contamination.

Activities of MDH were measured with a direct fluorometric procedure [21].

Statistical comparisons employed t-tests.

Results

Two days after exposure to the loud tone, amino acid concentrations in the exposed-side DCN of hamsters, in which increased spontaneous activity had been documented, were not different from those in the contralateral DCN except for higher glutamate and slightly higher GABA in the exposed-side molecular and fusiform soma layers and slightly lower taurine in the molecular layer (Table 1). The differences for glutamate and GABA were also found in control hamsters whose DCNs had been recorded from in physiological experiments and were absent in hamsters, either exposed or control, that were not used in physiological experiments (Table 2). We therefore concluded that they resulted from some aspect of the physiological recording and not from the loud tone exposure. Whereas the small taurine difference was not found in physiologically-studied control hamsters, it also was not found in exposed hamsters which were not physiologically studied. We therefore concluded that this marginally significant difference probably occurred by chance. There were some small bilateral differences between exposed and control hamsters, but most of these were not very consistent across the groups of animals and DCN layers (Tables 1 and 2). The most consistent were those for glutamate, glutamine, and taurine, which were usually slightly lower in exposed hamsters.

One month after exposure to the loud tone, there were again no large differences in amino acid concentrations between exposed-side and contralateral DCN (Table 3). As at 2 days of survival, the higher glutamate concentrations in the exposed-side DCN were present in control as well as exposed hamsters, and therefore did not result from the loud tone exposure. Concentrations of aspartate, glutamate, glycine, taurine, serine, arginine, threonine, alanine, and tyrosine were usually slightly lower in DCN layers of exposed than of control hamsters. This suggests possibly a rather general depression of amino acid metabolism one month after loud tone exposure.

At one month after loud tone exposure, there was no evidence for any change in oxidative metabolic capacity, as expressed by MDH activity, in the hamster DCN (Table 4).

Results for the layers dissections, or for dissections of tissue slabs oriented along the tonotopic axis of the DCN, have so far not revealed chemical differences between left and right sides of exposed hamsters, or between exposed and control hamsters, that are localized along the medial-lateral axis of the DCN similarly to increases of spontaneous activity [4].

Table 1 Amino acid concentrations in DCN layers of loud-tone-exposed and control hamsters with 2-day survival and recordings from the left DCN

| Molecular layer | | Glu | Gln | Gly | GABA | Tau | Ser | Arg | Thr | Ala | Tyr |
|----------------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|------------|------------|-------------|------------|
| Exposed L | Mean | 55.2 | 49.0 | 28.8 | 11.5 | 24.1 | 9.2 | 2.4 | 6.0 | 7.4 | 3.4 |
| | SEM | 3.1 | 3.2 | 1.1 | 0.4 | 1.2 | 0.7 | 0.2 | 0.6 | 0.6 | 0.5 |
| | N | 18 | 9 | 17 | 18 | 18 | 17 | 17 | 17 | 0.5 | 17 |
| Exposed R | Mean | 37.1 | 48.3 | 28.9 | 10.2 | 27.9 | 10.3 | 2.2 | 5.9 | 6.4 | 3.2 |
| | SEM | 1.0 | 1.7 | 1.0 | 0.4 | 1.3 | 0.8 | 0.2 | 0.4 | 0.3 | 0.3 |
| | N | 18 | 9 | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 |
| Control L | Mean | 53.5 | 52.3 | 27.2 | 12.0 | 28.4 | 8.9 | 2.1 | 4.3 | 10.6 | 4.2 |
| | SEM | 4.6 | 3.0 | 3.1 | 1.7 | 1.9 | 0.8 | 0.2 | 0.8 | 1.8 | 1.3 |
| | N | 6 | 6 | 5 | 6 | 6 | 5 | 5 | 5 | 5 | 5 |
| Control R | Mean | 41.5 | 58.4 | 29.9 | 10.4 | 29.0 | 10.5 | 1.9 | 4.7 | 9.3 | 3.1 |
| | SEM | 2.3 | 5.0 | 2.5 | 0.9 | 2.1 | 1.2 | 0.2 | 0.4 | 1.5 | 0.7 |
| | N | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Fusiform soma layer | | Glu | Gln | Gly | GABA | Tau | Ser | Arg | Thr | Ala | Tyr |
| Exposed L | Mean | 42.1 | 45.8 | 32.3 | 12.2 | 18.3 | 7.7 | 2.0 | 5.3 | 6.2 | 2.9 |
| | SEM | 1.5 | 2.1 | 1.2 | 0.5 | 1.1 | 0.5 | 0.1 | 0.3 | 0.5 | 0.3 |
| | N | 18 | 9 | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 |
| Exposed R | Mean | 36.1 | 45.6 | 35.1 | 10.6 | 19.8 | 8.2 | 1.9 | 5.5 | 5.6 | 3.4 |
| | SEM | 1.0 | 1.8 | 1.5 | 0.5 | 0.9 | 0.5 | 0.1 | 0.4 | 0.7 | 0.4 |
| | N | 18 | 9 | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 |
| Control L | Mean | 43.9 | 54.7 | 32.3 | 12.8 | 22.3 | 9.2 | 2.4 | 4.7 | 9.2 | 3.1 |
| | SEM | 2.5 | 2.5 | 2.5 | 1.5 | 1.6 | 0.5 | 0.4 | 0.3 | 0.8 | 0.5 |
| | N | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Control R | Mean | 36.9 | 53.7 | 37.3 | 10.7 | 18.5 | 8.2 | 2.2 | 4.4 | 7.5 | 3.3 |
| | SEM | 2.0 | 3.8 | 2.7 | 1.0 | 1.6 | 0.7 | 0.4 | 0.5 | 0.7 | 0.5 |
| | N | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| Deep layer | | Glu | Gln | Gly | GABA | Tau | Ser | Arg | Thr | Ala | Tyr |
| Exposed L | Mean | 34.1 | 39.8 | 27.7 | 7.7 | 12.3 | 6.3 | 1.9 | 4.3 | 4.8 | 2.4 |
| | SEM | 1.3 | 1.3 | 1.2 | 0.6 | 0.5 | 0.3 | 0.1 | 0.2 | 0.4 | 0.2 |
| | N | 19 | 10 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 |
| Exposed R | Mean | 32.4 | 37.5 | 30.1 | 7.9 | 13.0 | 7.0 | 1.9 | 5.1 | 4.5 | 3.0 |
| | SEM | 1.2 | 1.5 | 1.4 | 0.5 | 0.6 | 0.5 | 0.1 | 0.5 | 0.4 | 0.5 |
| | N | 17 | 7 | 15 | 16 | 17 | 15 | 15 | 15 | 15 | 15 |
| Control L | Mean | 37.2 | 52.0 | 30.6 | 9.3 | 15.6 | 8.1 | 2.5 | 4.5 | 7.7 | 3.0 |
| | SEM | 2.3 | 3.1 | 1.5 | 1.0 | 1.4 | 1.1 | 0.3 | 0.4 | 0.7 | 0.6 |
| | N | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Control R | Mean | 32.5 | 47.5 | 31.9 | 7.3 | 13.5 | 7.1 | 2.2 | 4.6 | 7.2 | 2.2 |
| | SEM | 2.8 | 3.7 | 2.4 | 0.8 | 0.9 | 0.8 | 0.4 | 0.8 | 1.2 | 0.4 |
| | N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

Abbreviations for amino acids are: Glu, glutamate; Gln, glutamine; Gly, glycine; GABA, γ -aminobutyrate; Tau, taurine; Ser, serine; Arg, arginine; Thr, threonine; Ala, alanine; Tyr, tyrosine.

Other abbreviations are: SEM, standard error of the mean; N, number of samples.

Discussion and conclusion

Despite the marked effect of loud tone exposure on spontaneous activity measured with multiunit recordings from the DCN [3,4], we have so far been unable to identify a chemical correlate for this physiological effect involving the major neurotransmitters of the cochlear nucleus: the amino acids glutamate, glycine, and GABA. This suggests that either these amino acid transmitter systems are not greatly involved in the activity change, or that the change involves alterations in other aspects of

their function, such as receptor sensitivity, release, or uptake. The lack of evidence for any change in oxidative metabolic capacity suggests that the increased spontaneous activity does not require a major increase in rate of energy supply to the neurons.

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Table 2 Amino acid concentrations in DCN layers of loud-tone-exposed and control hamsters with 2-day survival and no recordings made

| Molecular layer | | Glu | Gln | Gly | GABA | Tau | Ser | Arg | Thr | Ala | Tyr |
|----------------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|------------|------------|------------|------------|
| Exposed L | Mean | 40.1 | 43.4 | 27.9 | 12.2 | 25.5 | 9.7 | 1.8 | 7.2 | 6.3 | 3.6 |
| | SEM | 0.7 | 2.4 | 0.8 | 0.6 | 1.0 | 1.2 | 0.2 | 0.4 | 0.6 | 0.4 |
| | N | 12 | 3 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Exposed R | Mean | 37.9 | 39.3 | 26.3 | 12.7 | 24.9 | 10.1 | 2.2 | 7.0 | 6.4 | 4.5 |
| | SEM | 1.2 | 3.0 | 1.0 | 0.6 | 1.0 | 1.0 | 0.2 | 0.6 | 0.6 | 0.7 |
| | N | 12 | 3 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Control L | Mean | 47.6 | 49.8 | 26.3 | 13.3 | 31.8 | 9.2 | 2.5 | 8.1 | 7.5 | 3.8 |
| | SEM | 1.5 | 1.8 | 1.0 | 0.5 | 1.7 | 0.5 | 0.3 | 0.6 | 0.5 | 0.5 |
| | N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Control R | Mean | 48.5 | 49.6 | 26.6 | 12.6 | 33.1 | 9.4 | 1.6 | 6.9 | 6.2 | 3.6 |
| | SEM | 1.4 | 1.2 | 1.2 | 0.5 | 0.4 | 0.5 | 0.2 | 0.5 | 1.0 | 1.3 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Fusiform soma layer | | Glu | Gln | Gly | GABA | Tau | Ser | Arg | Thr | Ala | Tyr |
| Exposed L | Mean | 33.2 | 34.2 | 30.3 | 11.6 | 18.9 | 7.6 | 2.1 | 6.8 | 5.1 | 3.7 |
| | SEM | 0.9 | 1.6 | 1.2 | 0.5 | 0.6 | 0.6 | 0.2 | 0.5 | 0.6 | 0.6 |
| | N | 11 | 3 | 11 | 12 | 12 | 11 | 11 | 11 | 11 | 11 |
| Exposed R | Mean | 35.2 | 33.3 | 29.3 | 12.4 | 18.9 | 8.2 | 1.9 | 6.7 | 3.7 | 3.1 |
| | SEM | 1.3 | 1.0 | 1.2 | 0.4 | 0.7 | 0.9 | 0.2 | 0.4 | 0.4 | 0.3 |
| | N | 12 | 3 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Control L | Mean | 39.7 | 38.7 | 31.7 | 13.1 | 20.8 | 8.1 | 2.0 | 6.4 | 5.5 | 3.5 |
| | SEM | 0.6 | 0.4 | 1.7 | 0.7 | 0.8 | 0.5 | 0.3 | 0.3 | 0.5 | 0.3 |
| | N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Control R | Mean | 40.6 | 42.2 | 31.5 | 12.7 | 22.8 | 9.2 | 2.0 | 6.8 | 5.2 | 2.4 |
| | SEM | 1.8 | 1.2 | 1.8 | 0.3 | 1.3 | 1.5 | 0.3 | 0.4 | 0.7 | 0.3 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Deep layer | | Glu | Gln | Gly | GABA | Tau | Ser | Arg | Thr | Ala | Tyr |
| Exposed L | Mean | 28.9 | 30.3 | 29.4 | 9.0 | 13.3 | 7.7 | 2.3 | 5.9 | 5.2 | 4.5 |
| | SEM | 1.2 | 4.5 | 1.3 | 0.5 | 0.5 | 0.7 | 0.1 | 0.3 | 0.8 | 0.7 |
| | N | 12 | 3 | 11 | 12 | 12 | 11 | 12 | 12 | 12 | 12 |
| Exposed R | Mean | 30.4 | 26.6 | 23.1 | 8.2 | 12.2 | 6.4 | 1.6 | 4.9 | 3.3 | 2.1 |
| | SEM | 1.5 | 0.5 | 0.8 | 0.5 | 0.5 | 0.6 | 0.1 | 0.4 | 0.3 | 0.2 |
| | N | 12 | 3 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Control L | Mean | 37.1 | 35.0 | 27.7 | 9.4 | 15.7 | 6.0 | 1.9 | 5.8 | 4.9 | 2.4 |
| | SEM | 1.4 | 1.6 | 2.3 | 1.3 | 1.3 | 0.8 | 0.1 | 0.6 | 1.2 | 0.4 |
| | N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Control R | Mean | 33.7 | 36.0 | 30.8 | 9.8 | 16.0 | 8.0 | 2.0 | 6.2 | 4.6 | 2.3 |
| | SEM | 0.8 | 1.0 | 2.4 | 0.9 | 0.7 | 0.7 | 0.1 | 0.5 | 0.7 | 0.4 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

Abbreviations as in Table 1.

Table 3 Amino acid concentrations in DCN layers of loud-tone-exposed and control hamsters with 1 month survival and recordings from the left DCN

| Molecular layer | | Asp | Glu | Gln | Gly | GABA | Tau | Ser | Arg | Thr | Ala | Tyr |
|----------------------------|-------------|------------|------------|------------|------------|-------------|------------|------------|------------|------------|------------|------------|
| Exposed L | Mean | 7.9 | 43.0 | 33.0 | 23.5 | 10.6 | 21.9 | 5.5 | 1.8 | 3.9 | 6.1 | 2.1 |
| | SEM | 1.2 | 2.0 | 1.7 | 1.9 | 0.6 | 1.6 | 0.5 | 0.2 | 0.3 | 0.3 | 0.2 |
| | N | 19 | 20 | 20 | 20 | 21 | 21 | 20 | 20 | 20 | 20 | 20 |
| Exposed R | Mean | 5.9 | 31.6 | 28.1 | 19.8 | 8.7 | 19.6 | 5.0 | 1.5 | 3.6 | 4.8 | 2.1 |
| | SEM | 0.4 | 1.4 | 1.4 | 1.1 | 0.5 | 1.1 | 0.3 | 0.1 | 0.2 | 0.4 | 0.2 |
| | N | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| Control L | Mean | 9.7 | 49.6 | 32.6 | 27.9 | 8.9 | 23.8 | 8.8 | 3.5 | 5.2 | 6.5 | 3.8 |
| | SEM | 0.5 | 1.9 | 2.3 | 1.3 | 0.5 | 1.9 | 0.8 | 0.3 | 0.3 | 0.5 | 0.6 |
| | N | 14 | 14 | 8 | 14 | 14 | 14 | 14 | 14 | 14 | 14 | 14 |
| Control R | Mean | 7.5 | 37.6 | 33.6 | 28.4 | 8.9 | 27.6 | 9.1 | 2.6 | 5.6 | 6.2 | 3.1 |
| | SEM | 0.7 | 0.9 | 5.9 | 1.8 | 0.6 | 2.2 | 0.7 | 0.3 | 0.3 | 0.5 | 0.5 |
| | N | 15 | 15 | 9 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| Fusiform soma layer | | Asp | Glu | Gln | Gly | GABA | Tau | Ser | Arg | Thr | Ala | Tyr |
| Exposed L | Mean | 8.1 | 35.7 | 30.6 | 27.1 | 10.3 | 15.7 | 6.6 | 2.3 | 4.1 | 6.0 | 2.5 |
| | SEM | 0.4 | 1.4 | 1.0 | 1.3 | 0.7 | 0.9 | 0.6 | 0.2 | 0.3 | 0.3 | 0.2 |
| | N | 29 | 29 | 29 | 29 | 29 | 29 | 29 | 29 | 29 | 29 | 29 |
| Exposed R | Mean | 8.1 | 30.0 | 27.8 | 27.1 | 9.4 | 15.3 | 4.9 | 1.7 | 3.3 | 4.2 | 2.0 |
| | SEM | 0.6 | 1.5 | 2.0 | 1.5 | 0.5 | 1.3 | 0.6 | 0.2 | 0.3 | 0.5 | 0.2 |
| | N | 26 | 26 | 26 | 26 | 26 | 26 | 26 | 26 | 26 | 26 | 26 |
| Control L | Mean | 10.9 | 41.0 | | 29.2 | 9.8 | 17.2 | 7.2 | 2.7 | 4.8 | 6.0 | 3.2 |
| | SEM | 0.4 | 1.3 | | 1.4 | 0.8 | 0.9 | 0.7 | 0.2 | 0.3 | 0.6 | 0.5 |
| | N | 15 | 15 | | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| Control R | Mean | 10.0 | 34.7 | | 31.1 | 9.3 | 19.7 | 8.7 | 3.1 | 5.7 | 6.2 | 3.2 |
| | SEM | 0.9 | 1.6 | | 1.4 | 0.7 | 1.0 | 0.9 | 0.5 | 0.8 | 0.6 | 0.5 |
| | N | 14 | 14 | | 13 | 14 | 14 | 14 | 14 | 14 | 14 | 14 |
| Deep layer | | Asp | Glu | Gln | Gly | GABA | Tau | Ser | Arg | Thr | Ala | Tyr |
| Exposed L | Mean | 7.5 | 28.1 | 25.2 | 22.4 | 8.2 | 11.0 | 4.1 | 2.1 | 3.0 | 4.7 | 1.8 |
| | SEM | 0.3 | 0.8 | 0.8 | 1.4 | 0.7 | 0.6 | 0.3 | 0.2 | 0.1 | 0.3 | 0.2 |
| | N | 26 | 26 | 26 | 26 | 26 | 26 | 26 | 26 | 26 | 26 | 26 |
| Exposed R | Mean | 8.3 | 27.4 | 25.2 | 24.7 | 7.1 | 11.4 | 4.8 | 1.9 | 3.3 | 3.8 | 2.2 |
| | SEM | 0.7 | 1.4 | 1.8 | 1.8 | 0.4 | 0.8 | 0.5 | 0.1 | 0.3 | 0.4 | 0.2 |
| | N | 27 | 27 | 27 | 27 | 27 | 27 | 27 | 27 | 27 | 27 | 27 |
| Control L | Mean | 10.1 | 32.8 | 27.8 | 8.2 | 12.4 | 5.7 | 2.3 | 4.0 | 4.8 | 2.4 | |
| | SEM | 0.6 | 1.4 | | 1.3 | 1.4 | 0.6 | 0.3 | 0.1 | 0.4 | 0.5 | 0.3 |
| | N | 14 | 14 | | 14 | 14 | 14 | 14 | 14 | 14 | 14 | 14 |
| Control R | Mean | 9.3 | 29.4 | | 28.6 | 6.9 | 13.9 | 7.2 | 2.2 | 4.1 | 5.0 | 2.2 |
| | SEM | 0.7 | 0.7 | | 1.4 | 0.6 | 1.1 | 0.4 | 0.1 | 0.4 | 0.5 | 0.3 |
| | N | 13 | 13 | | 13 | 13 | 13 | 13 | 13 | 13 | 13 | 13 |

Abbreviations as in Table 1.

Table 4 MDH activities in DCN layers of loud-tone-exposed and control hamsters with 1 month survival and recordings from the left DCN. For control animals, data for left and right sides were combined to provide larger sample numbers since there was no obvious difference in MDH activity between them

| Layer | | Exposed | | Control |
|---------------|------|---------|-------|---------|
| | | Left | Right | |
| Molecular | Mean | 18.2 | 18.9 | 18.0 |
| | SEM | 1.3 | 1.3 | 1.1 |
| | N | 10 | 14 | 12 |
| Fusiform soma | Mean | 18.5 | 17.9 | 18.4 |
| | SEM | 1.4 | 0.8 | 1.1 |
| | N | 12 | 14 | 12 |
| Deep | Mean | 14.0 | 14.5 | 15.0 |
| | SEM | 0.8 | 0.9 | 0.8 |
| | N | 14 | 16 | 20 |

Abbreviations as in Table 1.

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Effect of emotional stress on auditory function in two strains of rats: An attempt for a model of hyperacusis

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Auditory evoked responses were measured chronically from right inferior colliculus in Lewis rats and Spontaneously Hypertensive Rats (SHR), to investigate a time-dependent effect of emotional stress on auditory function and susceptibility to noise. The two strains showed moderate differences in auditory threshold, but isolated stress induced larger amplitude of the positive component in Lewis rats. Furthermore, the combination of stress and acoustic trauma revealed differences in the short- and long-term, suggesting that the two categories of rats are not equally sensitive to plastic changes within inferior colliculus. In particular, an enhancement of amplitude was seen between 3 and 6 weeks in stressed SHR showing a persistent noise-induced threshold shift.

Introduction

Hyperacusis is frequently encountered in tinnitus patients, and according to Jastreboff [1] the two complaints are associated in as much as 40% of tinnitus sufferers. Even though tinnitus is usually the ground for seeking help, the coexistence of hyperacusis modifies the strategy for applying sound habituation therapy and needs to be taken into account when selecting noise generator level.

In the neurophysiological model of tinnitus generation and annoyance, subconscious part of central auditory pathways plays an important role [2]. In tinnitus sufferers as well as subjects complaining of hyperacusis, this area is likely to be influenced by emotional reactivity of the limbic system, and modifying the connections between the two systems is one of the major aims of sound habituation therapy.

It is well known that stressful events often enhance tinnitus loudness and/or annoyance, and may even trigger tinnitus generation. An unadapted reaction to stress thus appears as a potential predisposing factor for tinnitus and hyperacusis, acting either on their appearance or severity [3].

The present experimental study was undertaken to investigate whether differences in adaptation to stress were capable to modify central consequences of peripheral damage. Behavioral studies have

shown that Lewis rats and Spontaneously Hypertensive Rats (SHR) do not react similarly to stressful situations [4]. Therefore, the two categories of rats were compared in this report.

Auditory evoked potentials (AEP) from inferior colliculus were selected as objective tool for measuring auditory central function. This choice was based on preceding studies performed in acute conditions, showing enhanced amplitude of inferior colliculus after cochlear damage by noise or aspirine [5,6,7,8]. In addition to these findings, it appears that inferior colliculus is anatomically rather close to the limbic system, and could thus be one of the preferential site of interaction between auditory and limbic structures.

In contrast with previous studies using inferior colliculus for measuring auditory function, this report was based on chronic implantation in order to investigate the hypothesis of a time-dependent interaction between auditory function and adaptation to stress.

Methods

Forty male rats were assessed, including 19 Lewis and 21 SHR. The age at surgery ranged between 11 and 12 weeks to take account of two conflicting factors for the study, auditory maturation in the rat [9] and progressive deterioration of hearing in SHR [10].

Right inferior colliculus was selected for chronic

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implantation, using the technique recommended by the group of Salvi [11,12].

AEP were measured every week, from 80 dB SPL down to threshold, in the 0.25–25 kHz range. Left ear was used for sound stimulation.

Two weeks after surgery, the first AEP permitted to verify the quality of implantation.

Animals were then randomized into one of the following 4 subgroups: control, emotional stress, acoustic trauma, and a combination of emotional stress and acoustic trauma.

Emotional stress was realized by immobilization of the rat in a plastic bag for 2 hours, the animal being able to breath through a hole. Acoustic trauma was performed with a sweep between 8 and 16 kHz at 115 dB SPL for 2 hours.

Each animal was monitored over 6 weeks. An additional AEP measurement was performed just after acoustic trauma to differentiate between temporary and permanent threshold shift. In the combined group, noise exposure was carried out 6 days after emotional stress, the assumption being that it would take some time for the stress to induce plastic changes in auditory pathway and that these changes might modify susceptibility to later noise exposure.

Results

Analysis of variance (ANOVA) did not show dramatic effect of stress upon auditory function.

However, in the condition characterized by isolated stress the two strains of rats differed in their auditory responses at 80 dB SPL. When initial amplitude (week 1 of monitoring) was taken as normalized reference (100%), a progressive increase in the amplitude of the positive component was observed in the Lewis rats, whereas responses remained stable in SHR. In contrast with the group submitted to stress, control group showed stable responses in both SHR and Lewis rats, at least at most frequencies.

The difference seen between the two strains of rats (Lewis and SHR) in the stress condition varied from 40 to 100%, according to the frequency of stimulation and the week for measurement. The largest increase in Lewis amplitude was observed at 20 kHz, but substantial differences were also seen in the 3–8 kHz range. It should be noted that values of Lewis rats clearly exceeded those of SHR at all frequencies, although the former showed a larger inter-individual variability.

When stress was combined with noise overstimulation, results were more complex. Three types of findings were made. First, hearing threshold measured before acoustic trauma was approximately 5 dB worse in SHR than in Lewis, and this was observed at almost all frequencies.

Secondly, a short-term effect was noticed immediately after acoustic trauma. A threshold shift of 40–60 dB (above pre-exposure value) was observed in the two categories, Lewis and SHR. This threshold shift started at 6 kHz and was maximum in the 10–16 kHz range. Here again, as in the

pre-exposure measurement, threshold shift was larger (by about 10 dB) in SHR than in Lewis rats. In parallel with this short-term effect on threshold, amplitude showed immediately after acoustic trauma a larger notch in SHR group, i.e. amplitude of the positive component decreased more than in the Lewis group. This effect was seen at 8 kHz and above.

Thirdly, a long-term effect was noticed, developing between the 3rd and 6th week, where amplitude increased dramatically in SHR, the values exceeding those of the Lewis group. This was the only situation where the SHR overtook in amplitude the Lewis group. This enhancement in amplitude in the SHR group only occurred at frequencies showing a persistent threshold shift, i.e. from 12 kHz upwards.

Discussion and conclusion

This first study did not show clear-cut effect of stress on auditory function. However, some differences between the two strains, Lewis and SHR, were noticed. These differences were about hearing threshold and AEP amplitude, especially positive component. Interestingly, when stress was associated with acoustic trauma a sudden enhancement of amplitude was seen in one group (SHR) around the 3rd week, and this increase was restricted to the frequency range showing a persistent threshold shift. This finding supports the idea that peripheral damages are capable to induce plastic changes in inferior colliculus, and also suggests that these plastic changes could be facilitated by non-auditory factors such as adaptability to stress. Further studies are needed to better synchronize the action of emotional stress and acoustic trauma, and also to investigate the effect of these conditions on spontaneous activity within inferior colliculus in order to refine the knowledge of the pathophysiology of tinnitus.

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Altered spontaneous activity in rat dorsal cochlear nucleus following loud tone exposure

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Millions of people throughout the world suffer from tinnitus, about 62% of which is caused by loud sound exposure. In vivo electrophysiological studies using hamsters and rats have revealed increased spontaneous activity in the dorsal cochlear nucleus (DCN) following loud sound exposure. Behavioral tests suggest that these animals have tinnitus. This study investigated the effects of loud sound exposure on spontaneous activity of single units in the DCN. Under ketamine and xylazine anesthesia, young adult rats were exposed for 4 hours to an approximately 125 dB, 10 kHz tone presented directly to the left ear. Control rats were anesthetized in the same way as exposed rats but not exposed to the tone. Approximately 1–3 weeks after tone exposure, rats were anesthetized with sodium pentobarbital, decapitated, and brain slices prepared for in vitro electrophysiological recordings. Extracellular discharges of spontaneously active neurons in the DCN were recorded. The densities (units/penetration) of neurons and their firing patterns were analyzed. Three patterns of spontaneous activity were recorded: regular (simple spiking), irregular (simple spiking) and bursting (complex spiking). Increased proportions of bursting spontaneous activity and decreased proportions of regular spontaneous activity were observed in the brain slices of rats 7 to 23 days following loud sound exposure. These changes were more significant in the left DCN than in the right DCN. In addition, 18 neurons in the tone-exposed rat slices showed a long-burst pattern (more than 10 spikes/burst); only 4 neurons having such a pattern were recorded from the control rat slices. Previous studies have suggested that regular firing neurons include fusiform cells, and bursting neurons include cartwheel cells. Both these neuron types receive synaptic inputs from granule cells. The altered ratio of different patterns of spontaneous activity in the DCN might reflect the influences of loud sound exposure on the centrifugal and centripetal inputs to the granule cell population. Further studies are needed to investigate the changes in neuronal membrane characteristics and neurotransmitter receptors in the DCN associated with loud sound exposure.

Introduction

Tinnitus is the perception of sound in the absence of an acoustic stimulus. About twenty million people in the United States complain of tinnitus [1], although most people have this symptom at some time. Nine million people have severe or troubling symptoms [2]. About 62% of patients with severe tinnitus may have acquired it from exposure to excessively loud sound [3].

Understanding the mechanisms of tinnitus is the basis for effective treatment. These mechanisms have been suggested to be of both cochlear and central origin [4], and the existence of both types is

supported by substantial evidence. A cochlear origin is supported by the different distortion product oto-acoustic emissions of tinnitus sufferers compared to normal-hearing controls [5]. Observations on Ménière's disease, which is associated with endolymphatic hydrops, rupture of the membranous labyrinth of the cochlea, vertigo, hearing loss and tinnitus [6], also suggest a cochlear origin. Furthermore, among 151 selected tinnitus patients, two thirds reported complete relief of tinnitus after cochlear nerve section [7]. Substantial evidence also suggests central origins of tinnitus. One third of the above mentioned 151 tinnitus patients did not attain complete relief of tinnitus after cochlear nerve section [7]. Quinine and salicylates have long been known to cause tinnitus in humans. These agents have effects on cochlear [8] and central auditory structures, such as the auditory cortex and brainstem [9,10]. Using positron emission tom-

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ography (PET), increased regional cerebral blood flow in the association auditory cortex was demonstrated in tinnitus sufferers [11,12]. Studies also found that disturbances of brainstem auditory evoked responses in patients with tinnitus particularly affected waves I and III, but not wave II, and suggested the possible involvement of efferent pathways in the generation of tinnitus [13]. Several studies have suggested that both salicylate and intense sound can induce increased spontaneous activity in the central auditory system [14,15]. To date, there is still no mechanism that has become generally accepted.

The cochlear nucleus is the first brain center of the auditory system. It is divided into three sub-regions, the anterior ventral cochlear nucleus (AVCN), the posterior ventral cochlear nucleus (PVCN) and the dorsal cochlear nucleus (DCN). Fusiform cells of the DCN receive ascending inputs from auditory nerve type I spiral ganglion cells [16]. They are the main projection neurons of the DCN and provide a major input to the inferior colliculus. Regions of the DCN characterized by a high density of granule cells, may receive some ascending inputs from auditory nerve type II spiral ganglion cells [17,18,19]. The axons of granule cells form parallel fibers that synapse with cartwheel cells and fusiform cells [20]. Cartwheel cells are inhibitory interneurons occurring in large numbers in the superficial parts of the DCN [20].

Spontaneous activity is an important feature of the DCN both *in vivo* and *in vitro*. In the brain slice preparation, three types of spontaneous activity have been recorded from the DCN: regular, irregular, and bursting [21]. Regular-firing neurons include fusiform cells, and bursting neurons include cartwheel cells [22,23,24]. Waller and Godfrey [21] reported that, among 648 DCN neurons recorded in brain slices, 40% of spontaneously active neurons showed regular patterns, 30% showed irregular patterns, and 30% showed bursting patterns.

Using multiunit recordings, increased spontaneous activity in the DCN has been reported in hamsters [15] and rats [25] after exposure to high intensity tones. This study employed a brain slice preparation to compare the spontaneous activity in the DCN at the single unit level of normal and loud-tone-exposed rats. Recordings from DCN neurons showing different firing patterns have been used to relate the spontaneous activity with different morphological types of neurons. Information from single unit recordings will contribute to understanding effects of loud tone exposure on neuronal activity of the cochlear nucleus, and may contribute to understanding possible mechanisms of tinnitus caused by acoustic trauma.

Methods

Young adult Sprague-Dawley rats were anesthetized with ketamine (90 mg/kg) and xylazine (10 mg/kg), administered intramuscularly. During the 4

hours of tone exposure, the anesthetic was supplemented every hour and a half in order to maintain adequate sedation and analgesia. Following induction of anesthesia, each rat was mounted in a head brace and exposed for 4 hours to an approximately 125 dB, 10 kHz tone presented directly to the left ear. Control rats were anesthetized in the same way as tone-exposed rats for 4 hours without sound stimulation.

Approximately 1–3 weeks after tone exposure, rats were anesthetized with sodium pentobarbital (52 mg/kg, *i.p.*), decapitated, and the head rinsed in chilled artificial cerebrospinal fluid (ACSF). The brains were rapidly removed and bisected along the midline. The halves were trimmed and sliced transversely at 450 micrometers thickness with a McIlwain tissue chopper. Slices containing the cochlear nucleus were immediately transferred onto a nylon mesh in an interface chamber that was regulated at 32–34°C. The chamber was perfused with ACSF consisting of (mM) KH_2PO_4 1.25; KCl 5.00; MgSO_4 2.00; CaCl_2 2.00; NaCl 124; glucose 10; NaHCO_3 26. Temperature controlled humidified gas (95% O_2 /5% CO_2) flowed continuously over the slices in the chamber, and was also equilibrated with the ACSF solutions before use. After a recovery period (approximately 1.5 h), slices were explored extracellularly with glass micropipettes (1.5–2.5 μm tip diameter) filled with 1 M NaCl. The locations of penetrations were mapped onto a drawing of the slice, using the grid of the nylon mesh as a reference. Discharges of spontaneously active neurons in the DCN were recorded. The densities (units/penetration) and firing patterns of neurons were analyzed. Three patterns of spontaneous activity were recorded: regular (simple spiking), irregular (simple spiking) and bursting (complex spiking).

Results

Neuronal densities and proportions of neurons with different firing patterns

The neuronal densities in slices from control and loud-tone-exposed rats are shown in Table 1. The overall densities (units/penetration) for control rat slices were similar to those from rats 1 or 3 weeks after loud tone exposure when data from the three types of neurons were pooled together. For individual neuronal types, however, densities differed between the control slices and those from loud-tone-exposed rats. The densities of regular firing neurons were lower, and those of bursting neurons higher, in the slices from exposed rats than in control slices. These patterns were observed in both 1-week- and 3-week-survival groups, more significantly in the left DCN than in the right DCN (Table 2). The changes in densities of neuron types also showed as changes in the proportions of neuron types (Figure 1). The differences in neuron type proportions between control and exposed-rat slices were significant in the left DCN, but not in the right DCN.

Table 1 Densities^a of spontaneously active neurons in DCN slices from rats with 1 or 3 weeks survival

| 1 week | Regular | Bursting | Irregular | Total |
|--------------------------|--------------------------|-------------|-------------|-------|
| Control (8) ^b | 0.92 ± 0.48 | 0.80 ± 0.24 | 0.64 ± 0.24 | 2.36 |
| Exposed (8) | 0.56 ± 0.16 | 1.11 ± 0.39 | 0.48 ± 0.08 | 2.15 |
| 3 weeks | | | | |
| Control | 0.59 ± 0.11 | 0.74 ± 0.07 | 0.47 ± 0.11 | 1.81 |
| Exposed (8) | 0.35 ± 0.11 [*] | 1.10 ± 0.33 | 0.51 ± 0.08 | 1.96 |

^a Densities are represented as mean ± SD units/penetration.

^b Number in parentheses is number of rats for each group.

^{*} Difference between densities of regular neurons in control and exposed groups significant at $p < 0.03$.

Table 2 Densities^a of spontaneously active neurons in the left and right DCN slices of control and exposed rats

| Left | Regular | Bursting | Irregular | Total |
|--------------------------|--------------------------|-------------|-------------|-------|
| Control (8) ^b | 0.84 ± 0.30 | 0.58 ± 0.30 | 0.54 ± 0.27 | 1.96 |
| Exposed (8) | 0.38 ± 0.26 [*] | 1.07 ± 0.60 | 0.56 ± 0.25 | 2.01 |
| Right | | | | |
| Control (8) | 0.82 ± 0.71 | 0.84 ± 0.46 | 0.82 ± 0.64 | 2.48 |
| Exposed (8) | 0.55 ± 0.21 | 1.01 ± 0.53 | 0.46 ± 0.09 | 2.02 |

^a Densities are represented as mean ± SD units/penetration.

^b Number in parentheses is number of rats for each group.

^{*} Difference between densities of regular neurons in control and exposed groups significant at $p < 0.01$.

Mean firing rates of DCN neurons

The mean firing rates of DCN neurons in slices from the rats 1 week after loud tone exposure were similar to those from control rats. The firing rates of

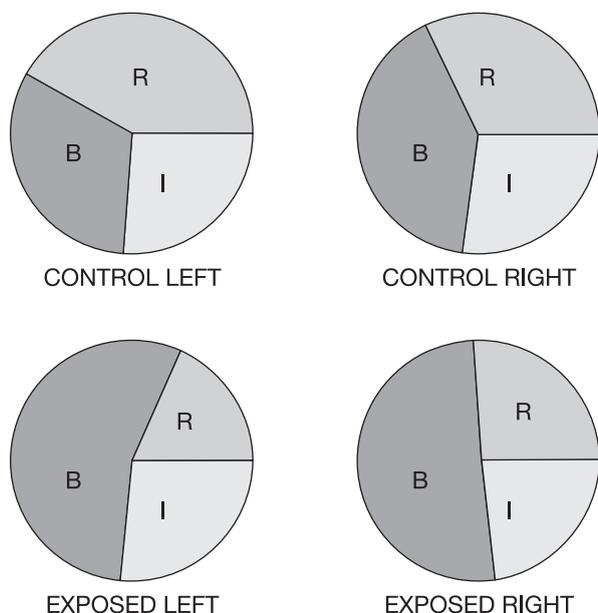


Figure 1 Proportions of different types of neurons in the left and right DCN of control and exposed rats. Data in each group include rats with both 1- and 3-week survival. The difference in relative incidence of the 3 types of neurons in the left DCN between control and exposed groups is significant at $p < 0.001$ (χ^2 test). B, bursting neurons; R, regular neurons; I, irregular neurons.

regular and bursting neurons in the slices from rats 3 weeks after loud tone exposure were significantly lower than those of control (Table 3). No significant difference was found between the left and right DCN (Table 4).

Table 3 Firing rates^a of DCN neurons from rats with 1 or 3 weeks survival

| 1 Week | Regular | Bursting | Irregular |
|---------|-------------------------------|-----------------------------|----------------|
| Control | 23.5 ± 11.4 (67) ^b | 4.2 ± 4.4 (54) | 5.8 ± 3.8 (41) |
| Exposed | 20.9 ± 7.7 (43) | 5.0 ± 4.9 (97) | 7.7 ± 5.4 (42) |
| 3 Weeks | | | |
| Control | 16.2 ± 5.7 [*] (47) | 6.0 ± 4.4 [*] (56) | 6.4 ± 3.8 (39) |
| Exposed | 13.5 ± 4.0 (25) | 4.4 ± 2.9 (83) | 6.6 ± 3.7 (39) |

^a Firing are represented as mean ± SD spikes/second.

^b Number in parentheses are number of neurons.

^{*} Difference between firing rates in 3 weeks control and exposed groups significant at $p < 0.03$ for regular and $p < 0.02$ for bursting neurons.

Differences in burst characteristics

Most neurons that showed bursting spontaneous activity had 3–5 spikes/burst, a pattern therefore considered typical. Four out of 110 (3.6%) bursting neurons in the control slices, and 18 out of 180 (10%) in the exposed-rat slices showed an atypical pattern characterized by prolonged bursts (more than 10 spikes/burst). The difference in the incidence of prolonged bursts between the control and exposed groups was statistically significant ($p < 0.05$, χ^2 test). Also, some very small neuronal activity was occasionally recorded in slices from exposed rats, but not in control slices. This was characterized by trains of very small spikes (about 50 μ V, Figure 2), usually too small for quantitative analysis, but easy to recognize with the audio monitor.

Table 4 Firing rates^a of neurons in the left and right DCN slices of control and exposed rats

| 1 Week | Regular | Bursting | Irregular |
|---------|-------------------------------|----------------|----------------|
| Control | 20.6 ± 11.4 (58) ^b | 5.4 ± 5.2 (46) | 6.0 ± 3.5 (37) |
| Exposed | 18.5 ± 7.6 (28) | 5.3 ± 4.7 (99) | 6.8 ± 4.8 (38) |
| Right | | | |
| Control | 20.5 ± 8.7 (56) | 5.0 ± 4.0 (64) | 6.1 ± 4.0 (43) |
| Exposed | 18.0 ± 7.5 (40) | 3.9 ± 3.0 (81) | 7.5 ± 4.6 (43) |

^a Firing are represented as mean ± SD spikes/second.

^b Numbers in parentheses are number of neurons.

Discussion and conclusion

This study employed an in vitro brain slice preparation to investigate the effects of loud sound exposure on spontaneously active neurons in the DCN at a single unit level. The overall densities of spontaneous activity in the slices from loud-tone-exposed rats were similar to or slightly lower than those from control slices. The overall mean firing rates of neurons in the exposed-rat slices were slightly lower than control. Thus, the overall spon-

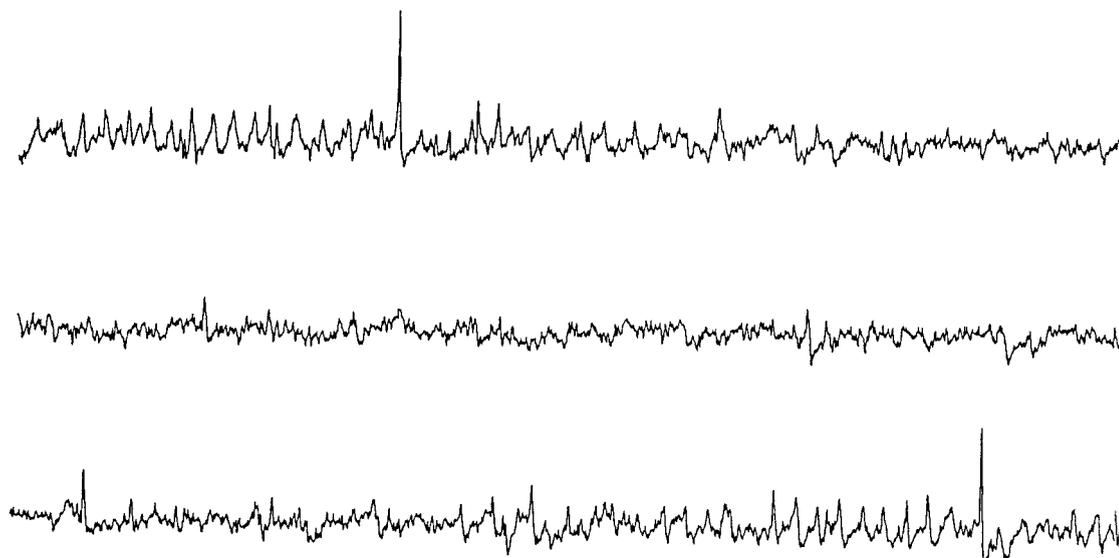


Figure 2 An example of the small-spike spontaneous activity recorded in a slice from a loud-tone-exposed rat. Train of small spikes can be seen in top and bottom rows. Each sweep represents 200 ms. The amplitude of the large spike is approximately 150–200 microvolts.

taneous activity of the exposed-rat slices was slightly lower, not higher than that of control slices. This differs from the results of *in vivo* multiunit recordings from hamsters [15], for which a 7–10 fold increase from the control level was reported, or from rats [25], for which a 140 to 240% increase from control was reported. This difference may result from the different tissue preparation (*in vitro* *vs.* *in vivo*), or recording methods (single-unit *vs.* multiunit) employed. Alternatively, perhaps the more prevalent small-amplitude bursting and prolonged bursting in slices from exposed rats are reflected as increased multiunit spontaneous activity *in vivo*. This study found, however, altered proportions of the different types of spontaneous activity. The fusiform cells of the DCN receive direct inputs from auditory nerve type I axons [16]. The decreased densities of regular neurons (including fusiform cells) in the loud-tone-exposed rat slices might result from transneuronal degenerative effects after acoustic over-stimulation [26,27,28] and/or from increased inhibitory inputs [29,30]. Because there is no known direct input from either the type I or type II auditory nerve fibers to the cartwheel cells, and because there may be little input from the auditory nerve type II axons to the granule cells [31], which provide a major input to cartwheel cells [32, 20], the increases in the densities of bursting neurons (most, if not all, probably cartwheel cells) might be related to an increased influence of centrifugal pathways to the cochlear nucleus.

Spontaneous activity in the DCN is relatively independent of the synaptic inputs from the cochlea [33]. Depending on animals' ages at treatment, cochlear destruction does affect the ventral cochlear nucleus neurons in their protein synthesis, cell size, and even cell number [34,35]. Whether the cochlear destruction has similar effects on the DCN is not known. Substantial evidence suggests that

DCN neurons are influenced by centrifugal pathways from higher centers in the auditory system, including auditory cortex [36,37], inferior colliculus [38,39], and superior olivary complex [40,41,42], as well as from non-auditory centers [43,44]. Excitation or inhibition of some DCN neurons by sound stimulation to the contralateral ear [45,46] also suggests effects of centrifugal pathways. The altered spontaneous activity reported in this study might reflect the influence of centrifugal pathways to the cochlear nucleus as a response to acoustic over-stimulation.

Although the mechanisms of tinnitus have been studied for a few decades, no proposed mechanism has become generally accepted. We suggest that tinnitus may be related more to changes in the centrifugal or descending pathways of the auditory system than to changes in the ascending pathways. The functional roles of the centrifugal pathways have not been extensively studied, but available evidence suggests that they may be involved in detection of signals in a noisy background [47,48], protection of the auditory system from acoustic trauma [49,50], and/or adjustments of sensitivity [51]. Tinnitus might result from a long-lasting change in the centrifugal pathways following acoustic trauma.

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Tinnitus in 7-year-old children

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Introduction

The incidence of tinnitus in children with normal hearing has been reported to be between 6 and 36% [1-4]. This could be compared to the incidence of tinnitus in the adult population that is said to be between 15 to 28% [5,6]. In children with hearing loss the incidence is reported to be much higher; up to 76% [1-4]. The variation between different studies is greater in children than in adults, which might depend on the difficulties faced when interviewing children. Children sometimes tend to try and please the investigators and answer in a way they believe they want them to. Due to these circumstances it is also important not to ask leading questions, particularly when interviewing children. Another problem with these kinds of interventions both for adults and children is that the respondents will sometimes get more focused on the symptoms being asked about, and it is important to be aware of this risk. To increase the reliability of the answers in the tinnitus interview, other authors only included children who at the beginning of the interview [1] had given reliable answers to practical questions, which did not concern tinnitus. By using this method between 6 and 13% of the children with normal hearing had experienced tinnitus. The variation depended on the criterion for response consistency.

Tinnitus severity in childhood is not extensively described. Predictors of severity of tinnitus in patients over 20 years of age have been described by many authors and in a recent review, psychological factors were found to be stronger predictors than hearing parameters [7]. There are some reports indicating similar findings for children as for adults with tinnitus [8,9]. It is suggested that chronic tinnitus in children should be regarded as a psychosomatic disorder and the diagnostic approach for this age group has to embrace organic, psychological and social aspects of the clinical history as well as audiometry [9].

Aim

The aim of the present study was to investigate the occurrence of tinnitus in 7-year-old school children

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by individual interviews and to, for each individual, relate tinnitus to noise exposure and hearing parameters.

Material and Methods

All 7-year-old school children are included in an audiometric screening procedure in Göteborg. A total of 964 consecutive children in this program were included in the study and were individually interviewed by an audiologist. Questions concerning experience of tinnitus and whether their tinnitus was related to noise exposure were included. If there were strong doubts concerning whether the child answered yes to the tinnitus questions in a reliable way, this response was considered as a no, f. ex. if the child first said yes and thereafter said no. Audiometric screening on 20 dBHL thresholds was performed on the frequencies: 0.5; 1; 2; 3; 4; 6; 8 kHz. The audiometer Ear Scan was used.

Results

There were a total of 964 children included in the study and 12% (n = 120) of the children experienced tinnitus. Only 12 of these 120 children had hearing loss defined as thresholds worse than 20 dBHL. Of these 12 children, 6 had conductive hearing loss (CHL), 4 sensorineural hearing loss (SNHL) and the remaining 2 had mixed hearing loss (MHL). The hearing parameters in the tinnitus and non-tinnitus group are presented in the table below. Only 2.5% (n = 24) had experienced tinnitus after noise exposure and only 3 of them had hearing loss (n = 1 SNHL, n = 2 CHL). In the total group of 964 children, there were 828 with normal hearing and the remaining 136 failed the hearing threshold of 20 dBHL. The incidence of tinnitus in 7-year-old school children with normal hearing was found to be 13%.

| | No tinnitus (n = 842) | Tinnitus (n = 119) |
|-----------------|---------------------------|-----------------------|
| PTA 0.5, 1, 2 R | 20.53 (± 3.0) | 20.39 (± 1.7) |
| PTA 0.5, 1, 2 L | 20.50 (± 2.6) | 20.23 (± 1.4) |
| PTA 3, 4, 6 R | 20.56 (± 3.7) | 20.27 (± 1.9) |
| PTA 3, 4, 6 L | 20.67 (SD: 3.8) | 20.22 (± 1.6) |
| Gender | 406 girls and 436 boys | 63 girls and 56 boys |

Statistical analyses including Pearson's correlation test; odds ratio and relative risk were performed. No correlation was found between perceived tinnitus and hearing parameters.

There were more girls than boys in the tinnitus group but the girls were not at a significantly higher risk for having tinnitus.

Multiple regression analyses were also performed with "tinnitus" as the dependent factor and pure tone thresholds for the low, mid and high frequencies, intratympanic pressure and gender as the dependent factors. None of these factors emerged as predictors for tinnitus in this study.

Discussion

An interesting finding was that there were more girls than boys who experienced tinnitus, however this difference was not statistically significant. This is in contrast to the incidence-ratio in adults in Sweden, where two thirds of the adult tinnitus complainers are men [5,7].

In the present study 12% of 7-year-old children experience tinnitus often or always (no: 120/964). In the normal hearing group the incidence was 13%. This is comparable to the findings of Stouffer *et al.* [1] where, of the children (n = 140) with reliable answers on practical test questions and normal hearing, 6 or 13% depending on the criterion for response consistency had tinnitus. In contrast to reports of increasing incidence of tinnitus among children with hearing loss which has been reported to be up to 76%, I did not find correlations of this kind. In the present study hearing parameters did not influence the occurrence of perceived tinnitus in this population.

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Children's experience of tinnitus

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Tinnitus has been much researched within adult populations [1,2,3], looking at prevalence, as well as its impact on individual's lives. Although the literature highlights the prevalence of tinnitus in children, there is little information on its effects from a psychological perspective. This small scale study looks at 24 children (50% with normal hearing and 50% with a hearing loss) who presented to the Psychology Department with troublesome tinnitus. In line with those adult studies, results suggest that tinnitus can have as marked an impact on children's lives as it is reported to have on adults. Insomnia, emotional distress, listening and attention difficulties, are the main psychological factors associated with tinnitus in children. These in turn may have an effect upon their school performance. Differences were found between children with normal hearing and those with some degree of hearing loss. Overall, children with normal hearing found tinnitus more troublesome, and presented with higher levels of anxiety than those with some level of hearing impairment. Our survey therefore suggests that children who complain of tinnitus should be taken seriously. In terms of management, individual intervention packages tailored to the needs of each child and family were found to be useful in alleviating anxiety and other associated factors.

Introduction

Studies have reported an incidence of tinnitus in hearing impaired children of around 55% [4]. Graham and Butler [5] found the incidence to be twice as high (66%) in children with mild to moderate hearing losses than those with severe to profound hearing impairment (29%). Research suggests that the incidence of tinnitus is more common in children with hearing impairments than in children with normal hearing. Stouffer *et al.* [6] in their study found approximately 1 in 4 hearing impaired children reported tinnitus, whilst an incidence of between 6% and 13% was found in normally hearing children.

A number of authors have suggested that children with tinnitus rarely complain about it and that they are more tolerant of a regular aural sensation than the adult population. The incidence of children spontaneously complaining of tinnitus has been placed at only around 3% [4], but when children do mention it of their own accord, it is likely that the tinnitus is troublesome and should be taken seriously [5]. Mills *et al.* [7], surveyed 93 normally hearing children, aged between 5 and 16 years. When directly questioned, 29% reported having "noises" in their ears, and nine children (9.6%) said that they were troubled by it.

Little is known however about the ways in which

tinnitus is troublesome for children, and the impact it has upon their lives. Graham [8] acknowledges that the degree of annoyance caused by tinnitus can be difficult to assess, but found that in one third of hearing impaired children in their study the tinnitus could be described as annoying. Martin and Snashall [10] completed a retrospective multicentre survey of 42 children who had attended an audiology clinic complaining of tinnitus. Approximately 50% of their population of children with tinnitus had normal hearing, and of the remainder, all degrees of hearing loss were represented. Overall, they found that 83% of the children reported their tinnitus as troublesome and a close relationship between tinnitus and other associated symptoms, i.e. dizziness and headaches was reported. Twelve of the children complained that tinnitus interfered with their sleep, 6 highlighted difficulties in concentrating, and stress or fatigue was reported by 5 children. They concluded that there is a small group of children for whom the experience of tinnitus is as severe as it can be for adults.

Drukier [9], reported that 70% of children with a severe to profound hearing loss had difficulties understanding speech when their tinnitus was present. This has been suggested to contribute to behavioural problems, including poor attentiveness and poor school performance.

Studies have looked at the impact of tinnitus upon adult sufferers. Tyler and Baker [1] in a survey of 72 adults with tinnitus found that it was associated with hearing difficulties in 53%, effects on life-style in 93%, general health in 56% and emotional difficulties in 70% of the sample. Getting to sleep was the most frequently mentioned difficulty and

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many respondents indicated that they experienced depression, annoyance, and insecurity. Complaints relating to sleep disturbance, auditory interference, and emotional distress have been consistently found in subsequent studies [2,3]. These now seem to be clearly established domains of complaint for adult tinnitus sufferers.

Method

A retrospective survey was carried out involving 24 children referred to the Psychology Department at the Nuffield Hearing and Speech Centre for help in managing their troublesome tinnitus. The children were referred by consultants in audiological medicine following physical examination. All children were accompanied by at least one parent for the initial assessment, where information was gathered about the child's life at home and at school during a clinical interview. More specifically, their experiences of tinnitus and how it impacted upon their lives was sought. Worries and anxieties about tinnitus were noted, and further intervention was given as appropriate.

Children were aged between 7 and 17 years (mean age 11.7 years), 50% of the children had hearing within the normal range, and 50% of the children had some degree of hearing loss. Of the children with a hearing loss, one had a unilateral profound loss; ten children had a mild to profound bilateral sensori-neural hearing loss; and one child had a conductive loss. Overall, sixteen children (67%) complained of intermittent tinnitus, while 8 children (33%), reported continuous tinnitus. (Table 1 indicates the breakdown between continuous and intermittent tinnitus for children with either normal hearing or with a hearing loss.)

Table 1 Tinnitus and hearing status

| | intermittent | | continuous | |
|----------------|--------------|--------|------------|--------|
| | n | (%) | n | (%) |
| Normal hearing | 9 | (37.5) | 3 | (12.5) |
| Hearing loss | 7 | (29.2) | 5 | (20.8) |

Almost half of the children (45.8%) had other health problems (as listed in Table 2), and five children of the total sample (20.8%) had additional specific or mild learning difficulties; eight children (33.3%) mentioned bullying; and three children had poor school attendance (12.5%). Thus (54.2%) of the total sample reported no additional educational difficulties.

Results

In line with adult studies, the main effects of tinnitus in children have been broadly categorised in terms of the effects on: hearing, listening and attention skills; tinnitus triggers and exacerbating factors; psychological effects and general health.

Table 2 Health problems

| Health problems | n | (%) |
|-----------------|---|--------|
| past meningitis | 3 | (12.5) |
| chronic fatigue | 3 | (12.5) |
| asthma/excema | 2 | (8.3) |
| thyroiditis | 2 | (8.3) |
| epilepsy | 1 | (4.2) |

Effects on listening and attention

Half of the normal hearing group described difficulties with attention and concentration, and with listening to the teacher (see Table 3). Within the hearing impaired group, a quarter of the children mentioned attention and concentration difficulties in school attributable to tinnitus. Approximately 40% of the normally hearing children reported listening difficulties at home, compared to 16% of children with a hearing loss. These difficulties at home, attributed to tinnitus by the children and parents, included listening to TV, music and conversations.

Table 3 Effects on listening and attention

| Listening and Attention Categories | Normal hearing | | Hearing loss | |
|------------------------------------|----------------|--------|--------------|--------|
| | n | (%) | n | (%) |
| listening at home | 5 | (41.6) | 2 | (16.6) |
| listening to teacher | 6 | (50.0) | 1 | (8.3) |
| background noise | 4 | (33.3) | 1 | (8.3) |
| attention and concentration | 6 | (50.0) | 3 | (25.0) |

Tinnitus triggers and exacerbating factors

The most commonly endorsed category of triggers for tinnitus was noise (45.8%), which included people shouting, music, vacuum cleaners, and classroom noise. Conversely, some children (24%) were more troubled by their tinnitus in quiet environments. Although age differences have not been reported, it was generally the older children who were able to identify particular emotional responses as triggers, whereas parents often identified this link for the younger children. These exacerbating factors included both immediate and longer term stressors such as school exams, anxiety, upset, parental separation and fear of the dark. (The full list of tinnitus triggers can be found in Table 4.)

Table 4 Tinnitus triggers

| Tinnitus Triggers | n | (%) |
|--------------------------------------|----|--------|
| noise (e.g. music, vacuum cleaner) | 11 | (45.8) |
| stress/anxiety/upset | 9 | (37.5) |
| quiet | 6 | (25.0) |
| removing hearing aids | 2 | (8.3) |
| physical (e.g. colds, jaw movements) | 2 | (8.3) |
| concentrating | 2 | (8.3) |
| other (e.g. travelling, warmth) | 6 | (25.0) |

Psychological effects

Only 25% of the children in the overall sample were reported, by parents and children, as having significant behavioural problems at home, such as tantrums and aggression. In contrast, fifteen children (62.5%) in the study were said to experience anxiety symptoms, including panic attacks, hyperventilation, fear of being alone, dizziness and preoccupation with their tinnitus symptoms.

Over half of all the children (54.2%), expressed specific worries or fears about their tinnitus, and similarly, the parental worries included concerns that tinnitus may be reflecting or even causing a deterioration in the child's hearing. Many of the older children reported similar worries to their parents, whereas the younger children's worries were generally around understanding why they had tinnitus. In some cases, the children personified the noises as, for example, a "scary monster" in their head or as people shouting. (Table 5 highlights the frequency of associated psychological factors between the two groups of children.) Parents also expressed concerns that the noises experienced by the children may be a sign of mental health problems, brain tumours, and other neurological conditions. Addressing these worries was a major part of our intervention with families.

There were roughly equal groups of children in the hearing impaired and normally hearing categories, who were annoyed about their tinnitus. Overall, approximately two thirds of the children (66.7%) reported "becoming ratty", "shouting at it", feeling fed-up, being frightened, and were generally annoyed by the presence of tinnitus.

Table 5 Associated psychological factors

| Psychological factors | Normal hearing | | Hearing loss | |
|-----------------------|----------------|--------|--------------|--------|
| | n | (%) | n | (%) |
| worries re: tinnitus | 7 | (29.2) | 6 | (25.0) |
| behaviour problems | 2 | (8.3) | 4 | (16.7) |
| anxiety symptoms | 12 | (62.5) | 3 | (12.5) |

Health

Overall, approximately 80% of children reported sleep difficulties which they attributed to their tinnitus. Most difficulty (reported by 66.7% of children) was experienced when getting to sleep, although some children also reported waking in the night (12.5%). There were no differences reported across the two groups of children.

Over 45% of the children reported physical symptoms associated with their tinnitus and/or hearing loss. Headaches were reported by approximately 30% of children, and dizziness by just over 16% of the sample, in each case with a roughly equal distribution between the two groups.

Management

At the time of the initial assessment, over 70% of children reported some form of coping strategy

which they had already discovered for themselves. Of the twelve children with a hearing loss, three felt that wearing their hearing aids enabled them to cope more easily with their tinnitus. Other coping strategies (Table 6) included covering, or putting their fingers in their ears, and taking cats or cuddly toys to bed.

Table 6 Coping strategies

| Coping strategies | n | (%) |
|----------------------|----|--------|
| tv/music/radio | 13 | (54.2) |
| ignoring/distraction | 9 | (37.5) |
| reading | 5 | (20.8) |
| wearing hearing aids | 3 | (12.5) |
| other | 10 | (41.7) |

Of the total sample, three families did not attend further appointments for treatment, thus the sample for ongoing treatment was 21 children. For most of these children, intervention techniques were used (Table 7) from more than one category, depending upon the nature of the main concerns, and appropriate to individual need. A range of psychological interventions were applied including Counselling, Cognitive Behaviour Therapy, and Systemic Therapy. Nearly 40% of the sample also required intervention around educational concerns.

Table 7 Management strategies

| Management Techniques | n | (%) |
|---|----|--------|
| Psychological therapies | 14 | (66.7) |
| tape/relaxation/imagery | 7 | (33.3) |
| practical advice | 6 | (28.6) |
| educational assessment and school input | 8 | (38.1) |

Discussion and conclusion

Results suggest that tinnitus can be a cause of great distress and worry both for children and their families. In line with Tyler and Baker's study [1], the biggest impact upon children's lives was found to be sleep disturbance, with over three quarters of the children reporting this as their main concern. It is also interesting to note that only 25% of children were reported as having behavioural problems, although almost two thirds of the sample of normally hearing children showed clear symptoms of anxiety. Although this group of children appear to show signs of distress more through internalising their feelings rather than through externalising behaviours, more research is needed to clarify this relationship.

For almost half of the normally hearing children, additional complaints included: difficulties listening both at home and at school; difficulties with background noise; attention and concentration difficulties in school. Children with a hearing loss reported less difficulties in these domains, which was an unexpected finding. One possible explanation may be that children with some degree of hearing

impairment may be more accustomed to auditory disturbance and thus find the impact of tinnitus less disruptive. This is a tentative finding on a small sample of children, and future research will hopefully help to shed further light on this observation.

Just over half the sample of children reported specific worries about tinnitus, for example that it might be damaging, or reflecting a deterioration in their hearing. These fears were equally shared by the parents. In some cases, children had personified their tinnitus noises into frightening characters, and thus working with children to alter their perceptions associated with these noises was an active part of our management. It was difficult to estimate the onset point, or the frequency of tinnitus in most children, as the younger children were unable to give reliable estimates of time.

From our clinical experience, tinnitus symptoms often decrease when other presenting difficulties are addressed (e.g. sleep, school difficulties, attention and listening skills, physical symptoms). For example, bullying was an issue for some children, and often the bullies would deliberately make loud noises to torment the child. Noise, absence of noise and stress were the most frequently cited factors associated with the onset of an episode of tinnitus. These were often mentioned as precipitating the onset of an episode of tinnitus in schools, e.g. absence of background noise during tests or work periods. Conversely, high levels of noise in the playground, scraping noises or school bells were also mentioned by children. Helping teachers to understand each child's individual difficulties, often resulted in positive changes to classroom management.

It was heartening to see how many children were able to employ their own coping strategies and to use imagination and visual imagery techniques to help combat their fears. Children of all ages in the study were seen to be helped by a greater understanding of their tinnitus; and reassurance about the nature of tinnitus played an important part in the therapeutic management for the whole family.

From this small scale study it would seem that tinnitus can have a marked effect on children's lives. When children report tinnitus as troublesome, their concerns should be taken seriously, and intervention can be beneficial for both the children and their families. In general, we can tentatively conclude that children's experience of tinnitus is broadly the same as it is reported for adults. These experiences

include sleep disturbances, anxiety, fear and worry, physical symptoms and auditory interference affecting both school and home environments. It would be valuable if future research could look in more depth at potential differences between children with a hearing loss, and children with hearing in the normal range. Similarly, more clarification is needed with regard to the relationship between tinnitus and other presenting difficulties. For example, from our study and clinical experience, it is clear that stress and anxiety play a large part in the lives of children with bothersome tinnitus. The causal relationship of this is as yet unknown and may help us to understand the reported differences between the two groups of children in this study.

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Neurovascular decompression of the eighth cranial nerve in patients with hemifacial spasm and incidental tinnitus

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Object: In order to clarify the characteristics of tinnitus due to neurovascular compression (NVC) of the 8th cranial nerve (8th N), we explored the 8th N in the cerebello-pontine cistern during neurovascular decompression (NVD) of the facial nerve in patients with hemifacial spasm who incidentally had tinnitus on the same side.

Methods: Between July 1974 and December 1998, we performed NVD of the facial nerve in 165 patients with hemifacial spasm, 12 of whom (9 women and 3 men; age range: 43–73 years) also complained of unilateral tinnitus on the same side as the spasm. We analyzed the preoperative characteristics of the tinnitus, surgical findings, and results of the operation in these 12 patients. To determine how many patients without tinnitus had NVC of the 8th N, we reviewed the surgical records and videotapes of surgery of 135 patients who had hemifacial spasm alone. The results were compared with those of patients with hemifacial spasm and ipsilateral tinnitus.

Results: NVC of the 8th N was confirmed in all 12 patients with hemifacial spasm who suffered from incidental tinnitus on the same side. This condition was found in only seven of 135 patients with hemifacial spasm alone, indicating that NVC of the eighth cranial nerve is one of the causes of tinnitus ($p < 0.001$, chi-square test).

The tinnitus resolved or was markedly improved after NVD of the 8th N in 10 patients (83%). Both pulsatile and continuous tinnitus responded well to NVD. All patients had sensorineural hearing disturbance of various degrees, but other neurootological examinations were of poor diagnostic value. It is our impression thus far that sensorineural hearing loss and positive findings on magnetic resonance imaging are the most reliable evidence for diagnosis of tinnitus due to NVC of the 8th N.

Tinnitus is associated with many pathological conditions [1–3]. The treatment of tinnitus, at present, is mainly palliative [2, 4–8], with destructive surgical treatment being used only in some intractable cases [3, 9–11]. Vascular compression of the 8th cranial nerve (8th N) has also been reported as a cause of tinnitus [12–23], but very few reports describe the characteristics of tinnitus caused by

vascular compression of the 8th N [19, 23, 24], making it very difficult to correctly diagnose tinnitus caused by neurovascular compression (NVC) of the 8th N. It is also almost impossible to predict whether tinnitus will resolve after neurovascular decompression (NVD), even if the patient presents signs strongly suggestive of NVC [14].

We realized that some patients with hemifacial spasm complained of unilateral tinnitus on the same side. We therefore explored the 8th N with the patients' consent when we performed NVD of the facial nerve (7th N) in patients who also had tinnitus. In this paper we report the results of exploration and NVD of the 8th N during decompression of the 7th N in those patients.

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Patients and methods

Between July 1974 and December 1998, we performed NVD of the 7th N in 165 patients with hemifacial spasm, 12 of whom (9 women, 3 men; age range: 43 to 73 years) also complained of unilateral tinnitus on the same side. Patients with hemifacial spasm sometimes experience tinnitus synchronized with facial spasm. This is caused by vibration of the eardrum as a result of irritation of the stapedius nerve within the 7th N. We excluded patients with this type of tinnitus from the present study. We analyzed the preoperative characteristics of the tinnitus, operative findings, and results of the operation in these 12 patients. All patients underwent full neurootological examinations preoperatively for both cochlear and vestibular function. The patients also underwent neuroradiological examinations including magnetic resonance imaging (MRI), computed tomography (CT), angiography, and air CT of the posterior fossa. The six most recent patients, however, underwent only MRI, which is noninvasive and thus far the most reliable imaging technique for the diagnosis of NVC [25, 26]. In order to study how many patients without tinnitus had vascular compression of the 8th N, we reviewed the operative records and videotapes of surgery of 153 patients who had hemifacial spasm alone. The results were compared with those of patients with hemifacial spasm and ipsilateral tinnitus.

Surgery

A small craniotomy of approximately 2.5×2.0 cm was made just behind the origin of the mastoid process with the patient in the lateral position. The cerebellum was gently retracted to expose the 7th and 8th N complex. The entire length of the 8th N in the CP cistern was carefully examined after completion of NVD of the 7th N. The 8th N was decompressed when NVC was detected. The offending vessels were gently displaced away from the nerve and attached to the adjacent dura mater using a small piece of oxycellulose soaked in Biobond® (Yoshitomi Pharmaceutical Industries, Ltd., Osaka, Japan) or fibrin glue. In patients with venous compression, the offending vein was coagulated and sectioned to free the 8th N. Special care was taken not to touch the 8th N and not to stretch the anterior inferior cerebellar artery (AICA) or internal auditory artery to prevent postoperative hearing disturbance. ABRs were monitored continuously during the procedure. If wave-V of ABR decreased in amplitude and became obscured, surgery was temporarily discontinued until it regained its normal shape. After completion of NVD of both nerves, the dura was closed in a water-tight fashion, and the bony defect was filled with bone chips.

Results

Operative findings

NVC of the 8th N was confirmed in all of the 12 patients. The offending vessels were the AICA in 4 patients, the posterior inferior cerebellar artery (PICA) in 2, the vertebral artery (VA) in 2, a vein in 2, a vein + AICA in 1, and the PICA + AICA in 1 (Table 1). Both the 7th and 8th N were compressed by the same vessel in 6 patients. In 2 patients the 8th N was compressed by two vessels and one of the two offending vessels was the same as the vessel found to be compressing the 7th N. The 7th and 8th N were compressed by different vessels in the other four patients. All offending arteries were displaced from the 7th and 8th N, and the veins were coagulated and sectioned successfully.

Table 1 Offending vessels for 7th and 8th N

| Case No. | Offending vessels for 8th N | Offending vessels for 7th N |
|----------|-----------------------------|-----------------------------|
| 1 | PICA | PICA |
| 2 | AICA | PICA |
| 3 | AICA | PICA |
| 4 | AICA | AICA |
| 5 | AICA + PICA | AICA |
| 6 | VA | VA |
| 7 | Vein | AICA |
| 8 | PICA | PICA |
| 9 | VA | VA |
| 10 | Vein + AICA | AICA |
| 11 | Vein | AICA |
| 12 | AICA | AICA |

PICA = posterior inferior cerebellar artery; AICA = anterior inferior cerebellar artery; VA = vertebral artery.

We reviewed the operative records and videotapes of 153 patients to study the frequency of NVC of the 8th N in patients with hemifacial spasm alone and were able to obtain precise information concerning the relationship between the 7th and 8th N complex and surrounding blood vessels in 135 patients. NVC of the 8th N was found in 7 patients (arterial compression in 6 and venous compression in 1), although they did not have any history of tinnitus. The occurrence of NVC of the 8th N in patients with tinnitus incidentally associated with hemifacial spasm was significantly higher than in patients with hemifacial spasm alone ($p < 0.001$, chi-square test).

Neurootological findings

Five patients had pulsatile tinnitus. The tone of the tinnitus was low-pitched in all 5 patients. The other 7 patients had constant or monotonous tinnitus, which was high-pitched in 6 and low-pitched in 1 (Table 2). The intensity of the tinnitus varied considerably from patient to patient. Two patients (cases 10 and 11 in Table 2) also had occasional rotatory vertigo lasting up to 30 min, and one of them was diagnosed as having Ménière's disease at an ENT clinic.

Table 2 Clinical background of patients with tinnitus incidentally associated with hemifacial spasm.

| Case No. | Age Sex | Side of T | Type of T | Caloric response | Nystag mus | OKN | ETT | ABR | SRT (dB) | Hearing loss (dB) | Pattern of hearing loss | History of T | History of HFS | Follow-up period | Outcome |
|----------|---------|-----------|-----------|------------------|------------|-----|-----|----------------|--------------|-------------------|--------------------------|--------------|----------------|------------------|-------------------|
| 1 | 68F | R | lp | n | n | n | n | n | 30 (30) | 40-60 (40-60) | 4-8 kHz (4-8 kHz) | 6M> | 3Y< | 14.1Y | disappeared |
| 2 | 53F | L | lp | n | n | n | n | n | 35 (35) | 30-40 (30) | all range (all range) | 3Y> | 10Y | 13.3Y | " |
| 3 | 43M | L | hc | d | n | n | n | delayed from I | 110< (35) | 90< (10-20) | 1-8 kHz (all range) | 8M> | 1Y | 13Y | markedly improved |
| 4 | 50F | R | hc | n | n | n | n | n | no data | 70-100 (45-55) | 4-8 kHz (4-8 kHz) | 3-4Y | 2Y | 10.8Y | unchanged |
| 5 | 67F | R | lp | n | n | n | n | n | 25 (25) | 20-40 (20-40) | all range (all range) | 3Y> | 3Y< | 10.7Y | disappeared |
| 6 | 73F | L | lp | n | n | n | n | n | 40 (40) | 60-70 (60-70) | 4-8 kHz (4-8 kHz) | 3-4Y | 10Y | 9.8Y | " |
| 7 | 44M | R | lc | d | n | n | n | delayed from I | 25 (20) | 15-30 (10-15) | all range (all range) | 1Y> | 7Y | 9.6Y | " |
| 8 | 70F | L | lp | n | n | n | n | n | 25 (20) | 50 (30) | 8kHz (8kHz) | 1.7Y | 1.7Y | 6.5Y | unchanged |
| 9 | 66M | L | hc | n | n | n | n | n | 40 (30) | 25-40 (20-30) | all range (all range) | 2M | 10Y | 3.8Y | disappeared |
| 10 | 65F | R | hc | d | n | n | n | n | 30 (25) | 30-40 (15-25) | 8 kHz (8kHz) | 8Y | 8Y | 3Y | " |
| 11 | 65F | R | hc | d | n | n | n | n | 30 (25) | 35-40 (35-40) | ≤0.5 kHz | 5M | 8Y | 3.4Y | " |
| 12 | 65F | L | hc | n | n | n | n | n | 20 (20) | 35 (35) | ≤0.5 kHz | 2Y | 5Y | 1Y | " |

T = tinnitus; R = right; L = left; lp = low-pitch pulsatile tinnitus; hc = high-pitch continuous tinnitus; hp = high-pitch pulsatile tinnitus; lc = low-pitch continuous tinnitus; n = normal; d = decreased; SRT = speech reception threshold.

All patients had various degrees of sensorineural hearing loss on both sides, but their hearing was more severely affected on the side of the tinnitus. Five patients had hearing loss in all ranges, 5 patients had high-frequency hearing loss, and 2 patients had low-frequency hearing loss. Speech reception threshold (SRT) was usually not affected very much even if hearing was mildly disturbed. A patient with a hearing loss of more than 90 dB had a SRT of only 30% at 110 dB (case 3 in Table 2). In 2 patients, ABR on the affected side showed prolonged latency from wave I, but in the rest of the patients there was no difference in latency between the affected and non-affected sides.

None of the patients had spontaneous nystagmus, and the results of the eye tracking test (ETT) were within normal range. In 2 patients the caloric response was slightly decreased objectively, and in two patients the decrease was so slight that it was detected only by the patients themselves.

Neuroradiological findings

In the early portion of this series we performed angiography and air CT of the cerebello-pontine cistern, but NVC of the 8th N was not confirmed in any of the patients. MRI was performed in the 6 most recent patients, and NVC of the 8th N was diagnosed by neuroradiologists in all 6 of them.

Operative outcome

All patients have been free of hemifacial spasm after NVD of the 7th N. Tinnitus has been completely resolved in 9 patients after NVD of the 8th N. In 1

patient the tinnitus diminished markedly, and in 2 of the patients the tinnitus remained unchanged. One patient experienced a temporary decrease in hearing of 20 dB, which gradually recovered to preoperative levels within 3 months (case 5). Sensorineural hearing loss did not improve after NVD in any of the patients. Two patients who had vertigo have been free of both vertigo and tinnitus (cases 10 and 11).

Discussion

The diagnosis of NVC of the 8th N is hardly ever made in patients with tinnitus since this condition has not yet been clearly defined, and there are no definite diagnostic criteria or operative indications for it at present. This makes it very difficult to obtain patients' consent to perform NVD of the 8th N for tinnitus, despite the fact that many of those suffering tinnitus refractory to drug therapy may have NVC of the 8th N. We noticed that some patients with hemifacial spasm complained of ipsilateral tinnitus unrelated to the spasm. Twelve of the 165 patients with hemifacial spasm whom we examined had unilateral tinnitus on the same side (7.3%). These patients were very valuable in terms of investigating tinnitus due to NVC of the 8th N.

Indeed, all 12 patients examined had vascular compression of the 8th N (100%), and the results of NVD of the 8th N were marked. Compression was found mainly on the caudal aspect of the 8th N when viewing the nerve through the retrosigmoid craniectomy. This compression site was confirmed to correspond mainly to the cochlear nerve by

monitoring the compound action potentials of the nerve, and also by MRI [11, 26, 27]. The tinnitus completely resolved or markedly improved in 10 of the 12 patients after NVD of the nerve (83%). On the other hand, a review of the operative findings in 135 patients who had hemifacial spasm alone, without tinnitus, showed that only 7 patients had vascular compression or contact with the 8th N. These findings indicate that vascular compression of the 8th N is one of the causes of tinnitus ($p < 0.001$, chi-square test).

The results of NVD of the 8th N for tinnitus in our patients were extremely good compared with those reported in the literature [14, 21]. Møller *et al.* [21] reported that 56.9% of their patients experienced only slight relief or no improvement in tinnitus at all. This difference is probably attributable to differences in the duration of the tinnitus. The mean duration of tinnitus in the slight improvement and no improvement groups was 5.2 and 7.9 years, respectively, in their report, whereas the mean duration of tinnitus in our patients was 1.8 years.

There is no clear definition of the type of tinnitus which is caused by NVC of the 8th N. Some authors have reported that pulsatile tinnitus is more likely to be due to NVC of the 8th N [19], while others have reported that high-pitched continuous tinnitus is attributable to NVC [20, 22, 24]. The present study showed that both continuous and pulsatile tinnitus responded well to NVD of the 8th N.

The 11 patients (92%) examined had bilateral sensorineural hearing disturbance of various degrees, with worse hearing on the side of the tinnitus in 7 of them. Sensorineural hearing disturbance was suggested as a possible initial sign of vertigo due to NVC of the 8th N [17, 22]. This may also be a very early sign of tinnitus due to NVC of the 8th N. Only 2 of our patients had abnormal ABR findings. SRT on the side of the tinnitus was normal or only slightly increased in 10 patients and markedly increased in 2. Most of the results of vestibular function testing were also normal except for a slightly decreased caloric response in 4 patients (Table 2).

It is our impression thus far that tinnitus due to NVC of the 8th N cannot be diagnosed based on neurootological findings alone, although it is necessary to accumulate more information to reach a definite conclusion.

The results of an MRI examination were very encouraging. MRI successfully disclosed NVC of the 8th N in our 6 most recent cases. We believe that MRI is the best auxiliary tool currently available for diagnosis of NVC of the 8th N [25, 26].

The characteristics of tinnitus due to NVC of the 8th N are very poorly understood at present. More information on this syndrome is needed to establish diagnostic criteria. We believe that accumulating evidence obtained in such cases as those described in the present paper will reveal the characteristics of tinnitus due to NVC of the 8th N and lead to the establishment of diagnostic criteria and indications for surgery.

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Effects of publicity on tinnitus

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This study looks at the effects of publicity self-reported by new patients presenting at tinnitus clinics, using a questionnaire. It studies data from 316 patients, taken from 4 centres, two private and two National Health Service. It was found that the 85% who had experienced publicity, more patients found publicity helpful than upsetting while some found it both helpful and upsetting. This paper summarises the explanatory comments which patients made, and also shows which style of publicity should be avoided.

Introduction

For several decades now vicious circles, or more correctly spirals, have been recognised in which tinnitus causes tension and anxiety, which then increases the tinnitus and causes more annoyance, and so on. Relaxation training and counselling has been used successfully to break those circles or spirals. More recently Jastreboff's neurophysiological model [1] and tinnitus retraining therapy [2] have been based on these aggravating but preventable and reversible chain of events. This has increased the recognition of the importance of reassurance and encouragement at the earliest possibility, and avoidance of gloomy and frightening publicity.

This study was actualised following some previous conflict of interest within the British Tinnitus Association's Management Council in 1995, regarding the type of publicity on tinnitus that it should produce itself, or promote or discourage from others. Some felt it necessary to 'dreadfulise' the worst case scenarios of tinnitus, perhaps to encourage more financial support for research and clinical services, and sympathy for those afflicted. The medical advisors felt this approach would simply feed the vicious circles and increase the distress of many people with tinnitus. In order to clarify the issue, this study was initiated by two of us, being British Tinnitus Association medical advisors.

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Method

A copy of the actual questionnaire is reproduced in the Appendix. It was given to each new patient at their first attendance at one of four tinnitus clinics over a period of 11–15 months centred on August 1996. The clinics were:

National Health Service:

| | |
|------------|------------------|
| Nottingham | n = 128 patients |
| Doncaster | n = 62 patients |

Private:

| | |
|------------|------------------|
| London | n = 103 patients |
| Nottingham | n = 23 patients |

The questionnaire asked if the patient had read or heard anything about tinnitus in the last one or two years, either on radio, TV, newspaper, magazine or from someone else or another source.

If YES, was it: helpful, or upsetting or worrying? If so, in what way? The patient was asked to describe in their own words what it was that helped or upset them.

Results

Three hundred and sixteen patients took part in the study. 166 male, 150 female. 85% (n = 269) reported having recently heard about tinnitus. The numbers of each source of information are shown in Table 1. Note that some patients reported more than one source.

Those answering YES indicated the following effects shown in Table 2.

The influences of gender, age, and type of patient were analysed, and Chisquared statistical tests

Table 1 Number of each source of publicity

| Radio | TV | Newspaper | Magazine | Someone else | "Somewhere" |
|-------|----|-----------|----------|--------------|-------------|
| 79 | 21 | 95 | 150 | 140 | 48 |

Table 2 Number indicating publicity was helpful and/or upsetting

| Helpful | Upsetting/Worrying | Both |
|------------------|--------------------|-----------------|
| 55% (n = 148) | 29% (n = 88) | 16% (n = 43) |

applied. Gender had no influence on the results. The elderly showed a non-significant trend towards having heard more about tinnitus in recent years, see Table 3.

Table 3 Reports of publicity – influence of age

| Age | 0–40 years | 41–60 years | 61+ years |
|------------|------------|-------------|-----------|
| Read/heard | 78% | 80% | 84% |

Age had no effect on whether publicity was helpful or not, but a non-significant smaller proportion of the elderly were upset by publicity, as shown in Table 4.

Table 4 Upset by publicity – influence of age

| Age | 0–40 years | 41–60 years | 61+ years |
|-------|------------|-------------|-----------|
| Upset | 38% | 35% | 26% |

The London group of private patients had a significantly ($p = 0.017$) greater awareness of tinnitus publicity.

The private tinnitus patients gave a significantly ($p = 0.023$) higher rate of having found publicity helpful. The data are shown in Tables 5 and 6.

Table 5 Report of publicity – influence of locality

| | Nottingham NHS | Doncaster NHS | Nottingham private | London private |
|------------|----------------|---------------|--------------------|----------------|
| Read/heard | 80% | 72% | 74% | 89% |

Table 6 Publicity helpful – type of patient

| | Nottingham NHS | Doncaster NHS | Nottingham private | London private |
|---------|----------------|---------------|--------------------|----------------|
| Helpful | 54% | 49% | 70% | 65% |

Amongst the 191 patients who found publicity helpful, the comments or explanations offered are shown in Table 7.

From the 121 patients reporting upset from publicity their comments/explanations have been grouped and are shown in Table 8.

Table 7 Aspects of publicity reported as helpful

| | |
|---|----|
| Helped them to understand tinnitus | 43 |
| Learning there were many other tinnitus | 35 |
| Learning: good prognosis, encouragement, reassurance, help and advice are available | 28 |
| Finding that there is possible treatment/management | 10 |
| Discovering a network of support | 9 |
| Research and clinical development is going on | 6 |
| Miscellaneous: advice on coping, management, etc. | 19 |

Table 8 Aspects of publicity reported as upsetting/worrying

| | |
|--|----|
| Told there is no cure | 41 |
| Fears of: possible serious disorder, progressive deafness, inability to lead a normal life | 11 |
| Told "little can be done" or "little known about tinnitus" | 10 |
| "You have to learn to live with it" | 5 |
| Interpreted publicity as inferring "it's all in the mind" | 3 |
| Horror stories and suicide (offset by one who found it helpful to hear how others suffered!) | 3 |

Discussion

Taking the significant results, together with the non-significant trends, we feel that this study suggests the following:

- The elderly have more time to read/watch TV and so may be more likely to see publicity about tinnitus.
- The elderly may be slightly less easily upset by the publicity due to having some general expectation of "wear and tear".
- The London group of private patients had a greater awareness of recent publicity, perhaps associated with a higher socio-economic status in that particular group of patients.
- The private patients in general found publicity helpful, possibly because of greater prior awareness of the importance of understanding tinnitus.

Conclusions

This study has identified the main aspects of publicity about tinnitus which patients find helpful, namely information and that there are many others with tinnitus.

It also shows the things that publicity should avoid, principally dwelling on the lack of cure, and failing to indicate that a lot can be done about tinnitus. Whenever possible we need to influence the media and self help organisations to give tinnitus the right kind of publicity.

- To give general information on tinnitus and what can be done to help.
- Encourage people, and not aggravate their tinnitus by emphasising the negative aspects.

Acknowledgements: The authors are grateful to Helen Spencer (Institute for Hearing Research Nottingham) for the statistical analyses.

QUESTIONNAIRE FOR NEW TINNITUS PATIENTS on TINNITUS PUBLICITY

Name of Clinic: Date seen:

Patient Initials: Sex: Age:

- 1. In the last year or two, have you heard or read anything about tinnitus:
 - On radio? YES/NO
 - On TV? YES/NO
 - In a newspaper? YES/NO
 - In a magazine? YES/NO
 - Somewhere, but can't remember where? YES/NO
- 2. Or has someone else told you about what they heard or read about tinnitus? YES/NO

Further questions if the answer to any of the above questions was YES

- 3. Did you find this publicity helpful to you? YES/NO
 - If "YES", in what way?
 -
 -
- 4. Did you find this publicity upsetting or worrying? YES/NO
 - If "YES", in what way and to what extent?
 -
 -

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Musicians and tinnitus

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Legislation concerning noise-exposed workers may exclude musicians. As a group, they are not often considered as noise exposed workers. However, as trained listeners exposed to high levels of noise and dependant on hearing [1] for the performance and enjoyment of their profession, musicians represent a unique noise exposed group.

To the musician the onset of a continual or intermittent tinnitus can have serious implications [2,3]. Results of a study covering a five-year period on a group of symphony orchestra players are presented. Hearing loss, tinnitus and hearing protection of musicians are discussed. Conclusions from this study indicate Distortion Product Otoacoustic Emissions (DPOAEs) are a useful screening tool, tinnitus can be an early indicator of hearing problems and using an industrial hearing conservation framework may be inadequate for the performing arts.

Introduction

With much emphasis in the literature on central processing and tinnitus sufferers, there is a danger of under playing the role of tinnitus as an indication of cochlear dysfunction. Noise is a major cause of hearing damage and tinnitus is often an early indicator of impending hearing problems [2]. Of all the occupational groups most likely to attend to the sound of their tinnitus, musicians would be expected to be highly troubled by the onset of tinnitus and pay more attention to it than other groups. It would therefore be highly desirable if a hearing conservation program was designed, which would detect small changes in hearing loss before they became a problem to the player. It was with these issues in mind that the tinnitus and hearing data from a group of symphony orchestra players was examined.

Methods

The sample of subjects in this study consisted of 41 symphony orchestra players who were tested in 1994 and again in 1998 and 1999 as part of their workplace hearing conservation program. Most players were exposed to an average of 24 hours of music at work per week. Four were part-time players and exposed to less than 24 hours and 10 subjects reported more than 30 hours of exposure per week due to teaching commitments and playing in

groups outside the orchestra. The musicians ranged in age from 25 to 60 years of age (Figure 1). To eliminate the effects of temporary threshold shift, players were required to have 16 hours of quiet prior to the assessment.

All audiologists, equipment and booths used in the testing program were approved and registered with WorkCover[†] as meeting or exceeding the standards described in the approved procedures [4]. Twin channel acoustic analyzer audiometers were used for testing hearing. GSI 38 Impedance meters were used to test middle ear function and GSI 60 distortion product otoacoustic emission equipment was used to obtain the otoacoustic emissions. The length of testing time allowed per musician was 45 minutes. During this time players were interviewed concerning the number of years playing, the exposure per week, the instrument played, instruments to the right and left and behind the player and other relevant audiological factors including the presence of continuous or intermittent tinnitus. The study was particularly interested in information concerning hearing loss, tinnitus and otoacoustic emissions and whether changes in any of these could be predicted in certain groups of musicians. Thresholds tested were 250 Hz, 500 Hz, 1 kHz, 1.5 kHz, 2 kHz, 3 kHz, 4 kHz, 6 kHz and 8 kHz. The method of testing was the Hughson Westlake Method of testing using ascending thresholds. Musicians were required to have otoscopic examination of their ears prior to testing to determine whether any temporary obstruction of the ear canal

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[†]Workcover is a West Australian government body that regulates the Worker's Compensation and Rehabilitation Act (1981).

| Age | Tinnitus detected | | | | | | | |
|---------------|-------------------|--------------|--------------|--------------|------------|-------------|-----------|---------------|
| | Absent | | Intermittent | | Continuous | | Total | |
| | Count | Row % | Count | Row % | Count | Row % | Count | Col % |
| 25 - 29 years | 6 | 100.0% | 0 | 0.0% | 0 | 0.0% | 6 | 14.6% |
| 30 - 34 years | 1 | 16.7% | 5 | 83.3% | 0 | 0.0% | 6 | 14.6% |
| 35 - 39 years | 2 | 22.2% | 6 | 66.7% | 1 | 11.1% | 9 | 22.0% |
| 40 - 44 years | 4 | 40.0% | 5 | 50.0% | 1 | 10.0% | 10 | 24.4% |
| 45 - 49 years | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| 50 - 54 years | 3 | 50.0% | 1 | 16.7% | 2 | 33.3% | 6 | 14.6% |
| 55 - 59 years | 1 | 50.0% | 1 | 50.0% | 0 | 0.0% | 2 | 4.9% |
| 60 - 64 years | 1 | 50.0% | 1 | 50.0% | 0 | 0.0% | 2 | 4.9% |
| Total | 18 | 43.9% | 19 | 46.3% | 4 | 9.8% | 41 | 100.0% |

Figure 1 Presence and Type of Tinnitus reported by musicians in each age group

was present which would prevent a valid test result. Impedance audiometry was also used to assess workers with middle ear conditions, which may affect the test results. Where this was detected, players were retested when the condition had cleared. If thresholds exceeded 25 dB, bone con-

duction thresholds were tested with masking if audiologically indicated. The cut off point for "normal hearing" was taken as 25 dB. A questionnaire was issued to the players prior to the 1994 test. This was a 7 page questionnaire and included the following questions about tinnitus (see Figure 1a).

At the conclusion of the appointment, the results of the audiological findings were discussed with each player individually, and the use of hearing protection was discussed. Any changes between the 1994 and 1998/99 results were also discussed. This was also the time for players to raise any concerns about their hearing.

Are you ever bothered by any of the following types of tinnitus/ringing in the ears?

a Spontaneous, "half-minute" tinnitus

| | | |
|----|-----|------------------------|
| NO | YES | Under quiet conditions |
|----|-----|------------------------|

How often? _____
 What Frequency? (pitch & octave)? _____
 Multiple? _____
 Describe _____

b Continuous

| | | |
|----|------------------------|---|
| NO | Under quiet conditions | Under normal work cond'ns (i.e. not quiet conditions) |
|----|------------------------|---|

What Frequency? _____

c Temporary - after performance?

| | |
|----|-----|
| NO | YES |
|----|-----|

Describe _____
 How long does it last? _____

Figure 1a Questionnaire for Musicians (1994)

Statistical analysis

The results obtained in 1998/1999 were compared with the musician's previous audiometric results obtained in 1994. The history was also compared to ascertain the percentage of musicians reporting tinnitus in 1999 compared with those reporting tinnitus in 1994. The musicians were further separated into five subgroups: group 1a, string players playing large stringed instruments; group 1b, string players playing small stringed instruments; group 2a, wind players playing large instruments; Group 2b represented the flute and piccolo wind instrument players and group 3, the percussion and brass players. The reason string and wind players were divided into subgroups was because it is known that the smaller string instruments, namely violins and violas, and the small wind instruments such as flutes and piccolos, can cause more hearing damage due to the high SPL's. Also these instruments are played

close to the player's ear [3]. The data for the subgroups was further analysed to determine which groups in the orchestra were showing signs of most fatigue in terms of both hearing loss and tinnitus.

Results

Figures 2 and 3 show the average audiogram for players in the 1994 sample and for players in the 1998/99 sample. Figures 4–12 show average audiograms and DPOAEs for subgroups.

The survey results from the 1994 questionnaire with 60 musicians are shown in figure 13. Overall, 33.4% reported tinnitus either intermittently or continuously (Figure 13). In the 1998/1999 group of 41 musicians, 56.1%, reported tinnitus either intermittently or continuously (Figure 14). Figure 15 shows tinnitus reported according to various

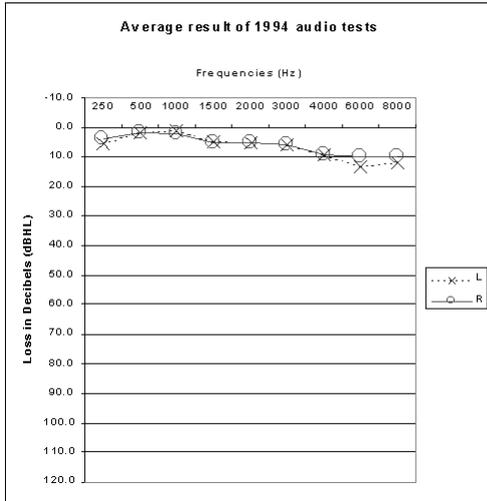


Figure 2 Average results of hearing tests for musicians in 1994 sample

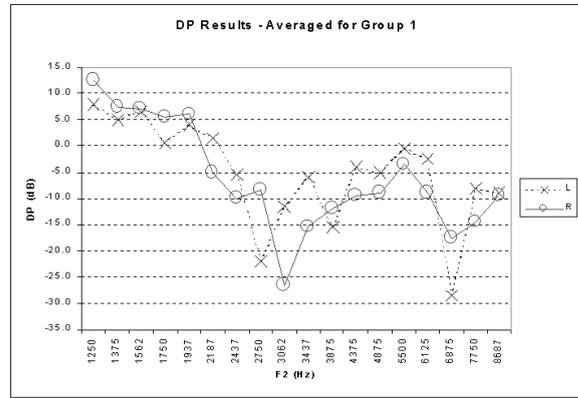


Figure 5 Distortion Product Otoacoustic Emissions results for musicians playing large instruments

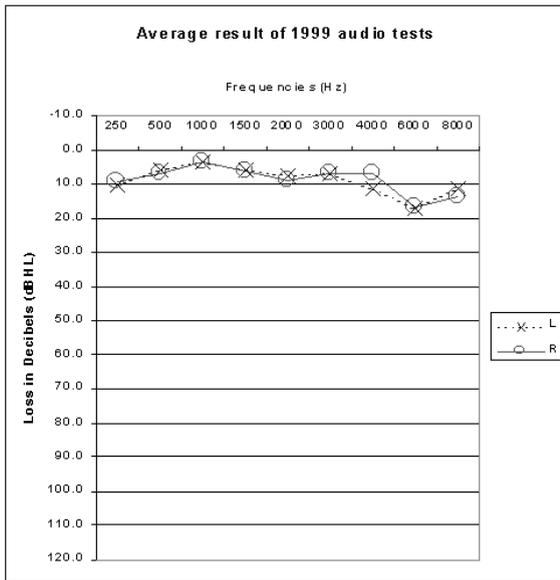


Figure 3 Average results of hearing tests for 1999 sample of musicians

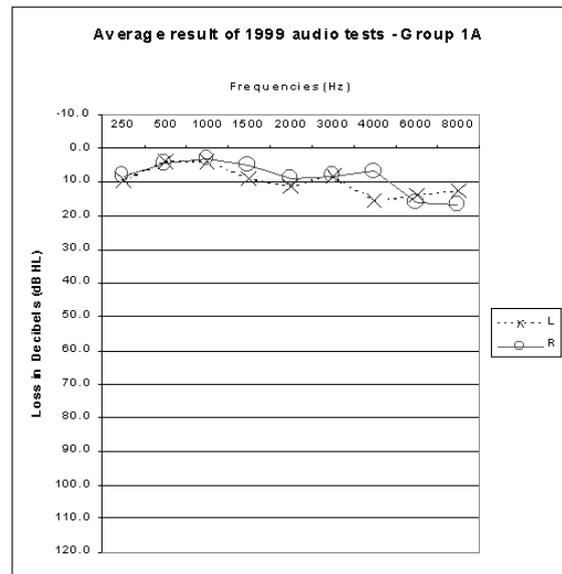


Figure 6 Averaged Audiometric results for players of violins and violas

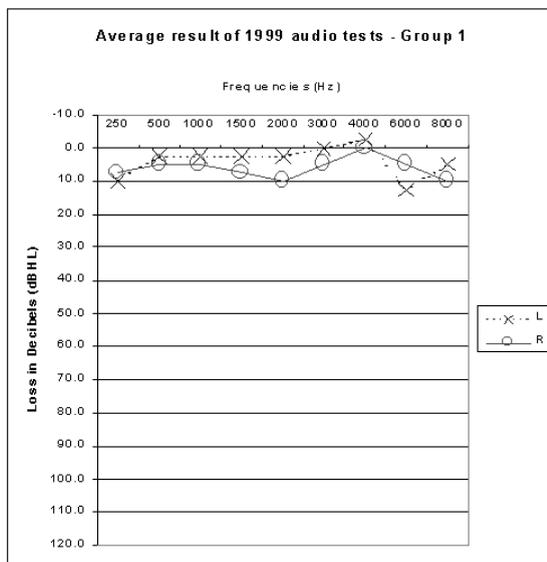


Figure 4 Results of audiometry for players of large string instruments

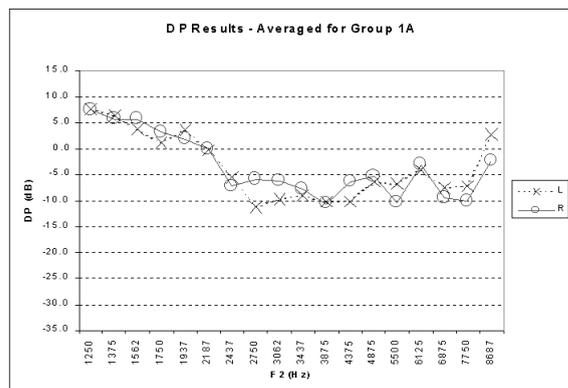


Figure 7 Averaged Distortion Product Otoacoustic Emissions for players of violins and violas

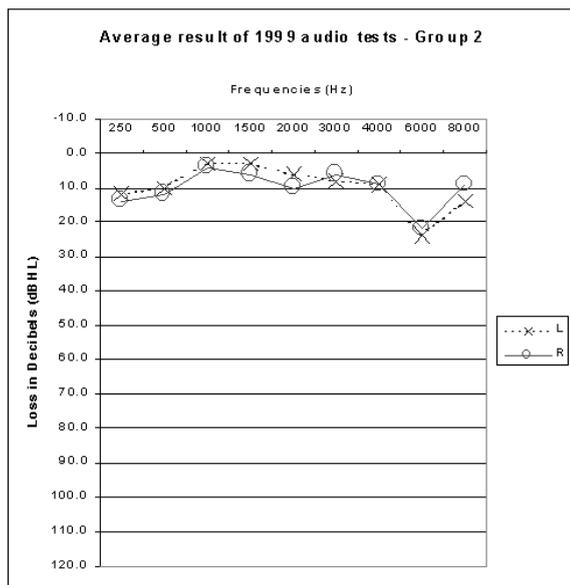


Figure 8 Averaged audiometric results for wind instrument players

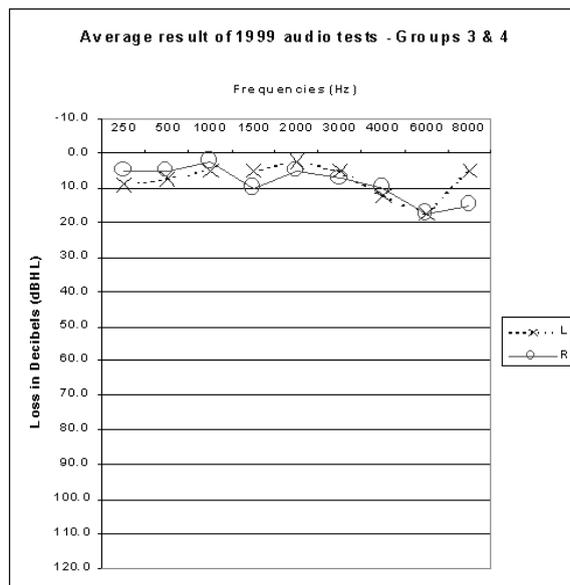


Figure 11 Averaged Audiometric results for percussion and brass players

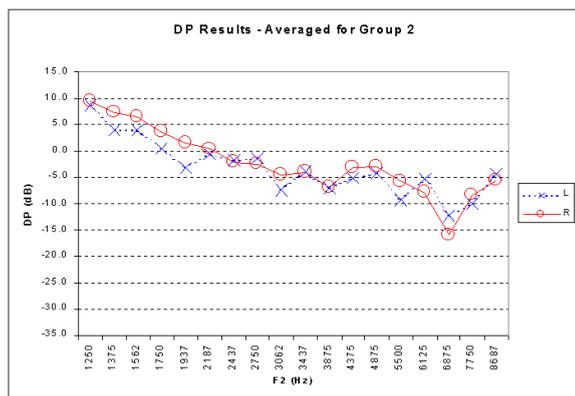


Figure 9 Averaged Distortion Product Otoacoustic Emission results for players of woodwind instruments

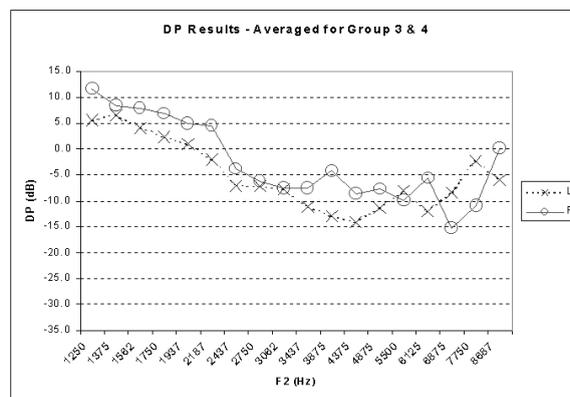


Figure 12 Averaged Distortion Product Otoacoustic Emission results for percussion and brass players

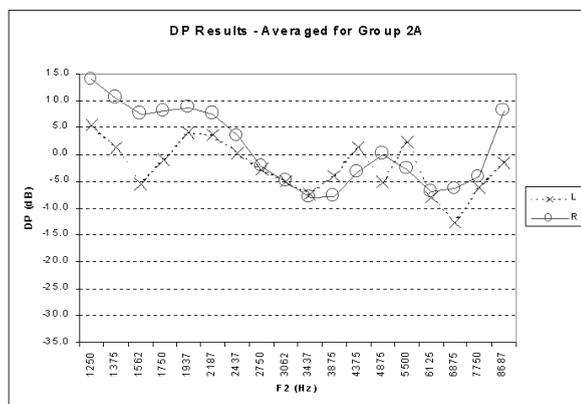


Figure 10 Averaged Distortion Product Otoacoustic Emission results for players of flutes and piccolos

subgroups of players. It is notable that three of the four players reporting continuous tinnitus played small string instruments. The fourth played bassoon and sat directly in front of the brass section.

The results of the tests performed on the 41 musicians were compiled into a database (Figure 16). Information on the musicians' backgrounds were recorded. The aim of the data analysis was to determine any factors related to the presence of tinnitus.

Tinnitus was recorded at 3 levels; non-existent, intermittent and continuous. The factors included for analysis are listed in Figure 16. The information concerning which instrument was played by each musician was included in the model via instrumental group. Also included in the model, as covariants were the musician's age, years of playing and hours of practice.

The results of an analysis of variance test are presented in Figure 17. A factor is considered to have a significant effect on the response variable (tinnitus) if its significance value (based on the calculated *F*

| Tinnitus | Count | % |
|--------------|-------|-------|
| Absent | 40 | 66.7% |
| Intermittent | 13 | 21.7% |
| Continuous | 7 | 11.7% |
| Total | 60 | |

Figure 13 All respondents of survey conducted in 1994

| Tinnitus | Count | % |
|--------------|-------|-------|
| Absent | 18 | 43.9% |
| Intermittent | 19 | 46.3% |
| Continuous | 4 | 9.8% |
| Total | 41 | |

Figure 14 Presence of Tinnitus (1999)

| Group | Tinnitus detected | | | | | | | |
|--------------|-------------------|--------------|--------------|--------------|------------|-------------|-----------|---------------|
| | Absent | | Intermittent | | Continuous | | Total | |
| | Count | Row % | Count | Row % | Count | Row % | Count | Col % |
| 1 | 1 | 20.0% | 4 | 80.0% | | | 5 | 12.2% |
| 1A | 8 | 57.1% | 3 | 21.4% | 3 | 21.4% | 14 | 34.1% |
| 2 | 6 | 54.5% | 4 | 36.4% | 1 | 9.1% | 11 | 26.8% |
| 2A | 1 | 33.3% | 2 | 66.7% | | | 3 | 7.3% |
| 3 and 4 | 2 | 25.0% | 6 | 75.0% | | | 8 | 19.5% |
| Total | 18 | 43.9% | 19 | 46.3% | 4 | 9.8% | 41 | 100.0% |

Figure 15 Tinnitus detection by instrumental group

statistic) is less than 0.05 (at the 95% confidence level).

The only statistically significant factor that

appears to influence tinnitus amongst the musicians in the orchestra is gender (Figure 18). Male players show a significantly higher likelihood of having tinnitus either intermittently or continuously.

Discussion

An independent noise survey taken at the various playing positions in the orchestra indicated that two

major areas of concern were the bassoons and clarinets [5]. These instruments are not excessively loud, however, the players were sitting in positions where other instruments were causing them problems. Overall the noise levels in the orchestra did not exceed safe levels by industrial standards and the results compare favourably with other studies [6,7,8,10].

Hearing loss

Hearing assessments for players in the 1994 and 1999 group showed no significant deterioration in thresholds. Reports of tinnitus in the 1998/99 survey showed 46.3% reported intermittent tinnitus

| Factor | Name | Value | Count |
|--|----------|--------|-------|
| Absence of OAES in high frequencies | ABS_OAES | No | 5 |
| | | Yes | 36 |
| Change in hearing | CHANGE | No | 30 |
| | | Yes | 11 |
| Gender | GENDER | Male | 26 |
| | | Female | 15 |
| Instrument Group | GROUP | 1 | 5 |
| | | 1A | 14 |
| | | 2 | 11 |
| | | 2A | 3 |
| | | 3 | 1 |
| | | 4 | 7 |
| Hearing loss detected | HL | No | 23 |
| | | Yes | 18 |
| Plugs worn | PLUGS | No | 24 |
| | | Yes | 17 |
| Considered at risk | RISK | No | 7 |
| | | Yes | 34 |

Between-Subject Factors used for the analysis.

Figure 16 Factors analysed

Tests of Between-Subjects Effects

| Source | Type III Sum of Squares | df | Mean Square | F | Sig. | Eta Squared | Noncent. Parameter | Observed Power |
|-----------------|-------------------------------|----------|----------------|--------------|-------------|----------------|-----------------------|-------------------|
| Corrected Model | 6.306 | 14 | .450 | 1.073 | .422 | .366 | 15.022 | |
| Intercept | .842 | 1 | .842 | 2.005 | .169 | .072 | 2.005 | |
| ABS_OAES | .004 | 1 | .004 | .100 | .754 | .004 | .100 | |
| CHANGE | .509 | 1 | .509 | 1.213 | .281 | .045 | 1.213 | |
| GENDER | 2.974 | 1 | 2.974 | 7.085 | .013 | .214 | 7.085 | |
| GROUP | .502 | 5 | .100 | .239 | .941 | .044 | 1.196 | |
| HL | .138 | 1 | .138 | .329 | .571 | .013 | .329 | |
| PLUGS | .164 | 1 | .164 | .391 | .537 | .015 | .391 | |
| RISK | .004 | 1 | .004 | .111 | .742 | .004 | .111 | |
| AGE | .271 | 1 | .271 | .646 | .429 | .024 | .646 | |
| HOURS | .226 | 1 | .226 | .537 | .470 | .020 | .537 | |
| YEARS | .742 | 1 | .742 | 1.769 | .195 | .064 | 1.769 | |
| Error | 10.914 | 26 | .420 | | | | | |
| Total | 35.000 | 41 | | | | | | |
| Corrected Total | 17.220 | 40 | | | | | | |

Figure 17 Results of the ANOVA with tinnitus as the dependant variable

| | Tinnitus detected | | | | | | | |
|--------|-------------------|-------|--------------|-------|------------|--------|-------|-------|
| | Absent | | Intermittent | | Continuous | | Total | |
| Gender | Count | % | Count | % | Count | % | Count | % |
| Male | 7 | 38.9% | 15 | 78.9% | 4 | 100.0% | 26 | 63.4% |
| Female | 11 | 61.1% | 4 | 21.1% | | | 15 | 36.6% |
| Total | 18 | | 19 | | 4 | | 41 | |

Figure 18 Tinnitus detectability and gender

and 9.8% reported continual tinnitus. Absence of tinnitus was reported by 43.9% of players.

The more objective measure of hearing loss was DPOAEs. Players' results on DPOAEs showed all but five players had some weak emissions in the frequency range 1 to 8kHz. With the exception of one musician, strong DPOAE's were consistent with no hearing loss and no tinnitus.

As noted by other researchers in this area, hearing loss in musicians was less than other occupational groups including mine workers and workers in noisy industries, however hearing was significantly worse than results for office workers [9]. With increasing hearing loss up to 10%, we see an increase in tinnitus to 50%, in industrial workers [11]. In our symphony orchestra population, no players had a 10% loss of hearing and yet 53% reported either continual or intermittent tinnitus. There could be a number of reasons for this including the musicians focusing on sound and the perceived threat that tinnitus poses to their profession and enjoyment [1,2,3,10]. Violinists show the greatest hearing loss on the left side, which can be due to the instrument being held on that side, whereas with the piccolo, because of the way the instrument is held, the right ear is more susceptible to hearing damage [1,3,10,12].

Exposure outside the workplace was reported by other studies as contributing to the condition of the musicians' ears [1]. The main exposure being teaching, which unless a player was teaching a percussion or brass instrument, was generally not a problem. Exposure to other loud instruments in the orchestra could account for problems in those players sitting directly in front of these instruments [1,3,8,12].

To assist in the prevention of hearing loss and tinnitus, a screening tool needs to be used that will detect loss before it becomes a professional and social problem [2]. For this reason otoacoustic emission testing was part of the test battery used in the study. It is no longer adequate to use audiometry as the first check in auditing hearing loss. Small changes to the integrity of the cochlea will be picked up sooner using otoacoustic emissions. In this study, otoacoustic emissions showed discrete changes to hearing and were useful when concerned musicians came in between their routine hearing checks, for example, after a particularly loud concert.

Compared with the general population and even the industrial population, the incidence of intermittent tinnitus was high in this group of players. (46.3% reporting some intermittent tinnitus). One reason may be that musicians are trained listeners and auditorily aware of their environment. In fact, diplacusis and tinnitus are seen as two threats to a musician's career [3].

Tinnitus

In this study the male players were more commonly exposed to woodwind, brass and percussion instruments. All female players played strings and woodwind instruments. Interestingly, players who reported no tinnitus and had good OAEs also reported wearing earplugs. Having good OAEs and no tinnitus was noted in all except one of the players. This player reported intermittent tinnitus in one ear only and interestingly the musician played a flute and it was the right ear, which was closest to the sound source which exhibited the intermittent tinnitus.

Of the four players with continuous tinnitus, three were in the string section. Two of the players reported continual tinnitus in the left ear only and they were both violinists. Violinists' left ears showed poorer results due to more exposure on the left side from their own instrument. This is consistent with results in other studies [11]. All four players with continual tinnitus were male. Players reporting intermittent tinnitus were scattered over all sections of the orchestra.

Hearing protection

Musicians were interviewed concerning instruments to the right and left and directly behind them. This study did not find an increase in the risk of sensory neural hearing loss for musicians situated in front of brass and percussion instruments. As an occupational group, musicians are very conscious of protecting their hearing. In our study, 41% of musicians reported wearing hearing protection at least in noisy passages in the music they played. As a group, any slight impairment of their hearing disturbed them. Generally, they sought quiet environments outside of work.

Raising the percussion and brass sections to higher levels is a practice adopted by many orchestras [6]. This lessens the SPL delivered to the ears immediately in front of these sections. Westmore notes that many brass players do raise their instruments during noisy passages [6]. In orchestras where this does not happen, there is friction between players. Increasing distance between players would help but this is not always practical. Decreasing reflecting properties on the stage and in the auditorium would also help but the overall sound quality for the audience may be diminished [6].

The hearing protection worn by the players was either the industrial type, hi-fi plugs or etymotic research plugs, ER15 and ER25s. The ER series, recommended for the string players, utilises an attenuator button plugged into a custom-made ear canal mould. The attenuator along with the volume of air in the bore of the ear mould serves to enhance the high frequencies. The overall effect is a flat response. For musicians such as violinists, the magnitude of the high frequencies are important, therefore the ER15s are recommended [3,12]. More attenuation in the high frequencies is required for percussion players and ER25s are recommended [3]. The vented tuned earplugs were designed for players whose instruments had less high frequency energy and protection was necessary but hearing the "interresonant breathiness" of the instrument was important. Industrial earplugs reduced high frequencies more than the musicians plugs, however, most musicians find they cannot tolerate losing this degree of high frequency information. Some musicians, who were not regular earplug users, used the industrial type earplugs, particularly for noisy pieces. Results from this study for players wearing plugs showed 9 of 16 players who wore plugs had no hearing loss. This shows the concern and seriousness players are taking to prevent hearing loss.

Where to from here?

Of paramount importance is knowledge of the acceptable noise levels and the need to rotate players so that time exposed is within acceptable levels [7]. Hearing testing is too crude to measure changes in hearing quickly enough to stop susceptible musicians from damaged hearing [2]. Hearing assessments should be more frequent than in industry, with more focus on the high frequencies. OAEs may have a place in early detection. This study showed that more discrete changes in hearing could be measured using DPOAEs. We found most players had reduced OAEs early in their careers. Musicians certainly appreciated an objective measure of their hearing being carried out and dips in OAEs gave an indication of the instruments that may be causing the problem. The hearing assessment allowed for time to discuss individually, the hearing protection needs of the player. In future studies, it would be interesting to know how many players are long term users of hearing protection and whether their results show less cochlear damage.

In reducing noise at its source, we may jeopardise the type and quality of the music played. Suggestions in other literature include having players on a stationary escalator type set up so that the sound from their instruments is projected out rather than into the ear of the player in front [1].

Legal aspects

Musicians who are exposed to high levels of noise are at risk of long term permanent hearing loss. Early detection and education about hearing protection and possible modifications to practice and performance venues may reduce or delay the onset of hearing loss and tinnitus.

Musicians know that they are likely to sustain damage to their hearing through their work with the orchestra. For some, the damage may be severe and effect them socially and economically. Formal measurements are necessary to detect hearing damage and measure any change over time. Formal measurements of hearing levels and documentation concerning tinnitus are necessary if players are to have the information required in a court of law if severe damage is sustained either at work or somewhere else. Basic information needs to be given to prevent noise induced hearing loss. Players need to know the warning signs and what to do in a dangerous situation. Tackling the problem at its source with custom-made plugs and through education about safe noise levels are all techniques cultivated from the industrial scene, however using an industrial hearing conservation program for musicians is an over simplification [2,8].

An employer of musicians could be deemed negligent if there is no evidence that reasonable steps are being taken to reduce the exposure, provide hearing protection, and implement hearing conservation programs including carrying out audiometric testing. Some of the repertoire of an orchestra may place the players at risk and an open approach between the players' union and management should be adopted.

Conclusions

With hearing loss virtually non-existent in the group, the reason why over half the players reported intermittent or continual tinnitus was unclear. Initially, investigation of the theory that musicians were trained listeners and would therefore notice tinnitus more readily than other groups was considered. Other studies reported less tinnitus incidence [12]. The otoacoustic emissions revealed interesting results. Strong otoacoustic emissions are displayed where there is little or no damage to the outer hair cells of the cochlea. Only five players had good otoacoustic emissions and all but one player reported no tinnitus. The otoacoustic emissions for most players showed that the musicians had considerable cochlear damage. The results support tinnitus being a good warning sign for musicians. The results also suggest that industrial standards for safe levels of

noise for workers are not necessarily satisfactory for the performing arts. Otoacoustic emissions are valuable in assessing the hearing of musicians, measuring subtle changes after a temporary threshold shift, alerting players to impending permanent damage and the reason why they are experiencing tinnitus. These measures reinforce in the player's mind the need to wear hearing protection even when they have good results on all the other tests.

Lower safe levels need to be set for the performing arts. Loud noise can not always be reduced at its source or acoustically in the playing environment, therefore the wearing of musicians earplugs needs to be encouraged [7,10,12]. Otoacoustic emissions should be part of regular hearing screening for musicians and hearing screening should take place more frequently than in industry. When a player observes the onset of tinnitus, or has other concerns with their hearing, further testing and counseling is essential.

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A case report: Gaze-evoked tinnitus

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Many factors are described as possible evokers of a subjective aural perception, tinnitus. We present two cases with the common characteristic that gaze changes can produce this sensation. Case 1 presents a gaze-evoked tinnitus after removal of acoustic neuroma of cerebellopontine angle. Case 2 describes a tinnitus with oscillopsia related to non-defined gaze changes or a conflicting vision situation. Possible central or peripheral mechanisms are exposed. Several treatment approaches are discussed.

Introduction

Literature [1,2] has described many factors as possible evokers of a subjective aural perception, tinnitus. We present two cases with the common characteristic that gaze changes can produce this sensation. Case 1 describes similar features as the ones published in the literature after removal of space occupying lesion of the cerebellopontine angle. Case 2 presents substantial differences in aetiology, associated symptoms and tinnitus manifestations.

Case exposition

Case 1: male, 33 years old. The patient was referred to our tinnitus clinic presenting a progressive unilateral (right) hearing loss since one year ago and spells of rotatory vertigo lasting 20 to 30 minutes in the last 3 months. Otoscopy, rhinoscopy and pharyngoscopy were normal. Neuro-otological exploration was normal too. Rinne test was positive for both ears, while Weber was more evident on the left side. Tympanometry and stapedial reflex was between normal ranges. Audiometry presented a mild high frequencies hearing loss in the right ear. (Figure 1). Maximal speech discrimination on right ear was 82%. Vestibular battery test (caloric-rotatory chair) showed a mild right labyrinth hyporeflexivity. Neither spontaneous nor positional nistagmus was found. ABR showed an increased right IV peak latency. MRI study presented a right cerebellopontine angle tumor (2.1 cm). Fifteen days later, a tumour was removed by a retrosigmoid sur-

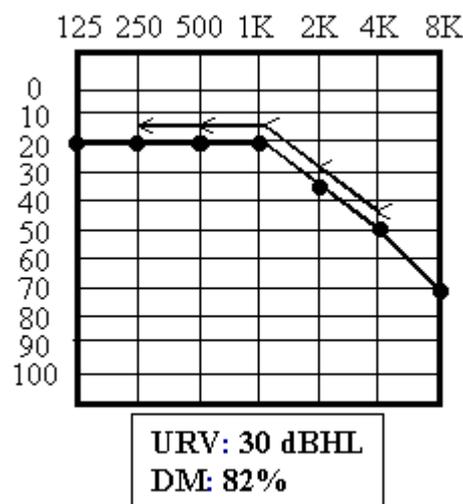


Figure 1 Right ear preoperative audiometry

gery approach. Pathology studies diagnosed a vestibular schwannoma.

One month following surgery, the patient starts with a gaze-evoked tinnitus on the right ear. Vertical deviation in eye direction (up and down gaze) can evoke a right side tinnitus for seconds. Patient can turn tinnitus on and off with eye movements, and it was absent when the eyes are in a neutral position. No other factors (light, head position, loud sounds) contribute to the apparition of tinnitus. Audimetry shows a cofosis in the right ear. Tinnitometry studies are as it follows: pitch 4000 Hz, loudness: 6 dB over threshold (no changes in intensity when the tinnitus was on), minimal masking levels (measured on the normal hearing ear) was 45 dB and residual inhibition was negative. Tinnitus Handicap Inventory 3 was scored on 48%, and tinnitus intensity according to a visual analogical scale (0–10) was 3.

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Patient is actually followed-up by the referring hospital.

Case 2. Male, 62 years old. Patient was referred to our tinnitus clinic presenting tinnitus on right ear since 4 months ago. Tinnitus appears many times a day (almost every hour) and last for seconds. Patient refers vertical movement of the objects, without rotatory sensation during the tinnitus period. Changes in non-defined eye direction, as a result of a conflicting vision seems to be the possible tinnitus evoker factor. Head movements are not related to tinnitus perception. After those periods, the patient is absolutely asymptomatic. Neither hearing impairment nor aural fullness is present. Patient refers a history of ischaemic heart disease, hypercholesterolemia and cervical arthrosis. Migraine is not present.

Otoscopy, rhinoscopy and pharyngoscopy are normal. Neuro-otological exploration is normal. Rinne test is positive and Weber does not show any predominant side. Pure tone and speech audiometry, tympanometry and stapedial reflex are between normal ranges. Tinnitometry shows a 4000 Hz pure tone pitch, loudness (6 dB over threshold), minimal masking level of 10 dB over threshold and positive residual inhibition during 40 seconds. Discomfort threshold levels are in a normal range. THI scores rises to 32% and intensity score is 3. ABR and otoacoustic emissions (spontaneous, evoked and distortion products) were between normal values. MRI of cranial structures and X-ray study on cervical spine column are normal vertebral and carotid eco-doppler study shows atheromatosis on internal carotid without significant stenosis. Vestibular battery test (caloric-rotatory chair) presents a mild hypo-reflectivity on right posterior labyrinth, and left spontaneous nistagmus, grade I. The oculomotor system is between normal limits. Dynamic posturography presents a vestibular pattern (conditions 5 and 6 of the Sensory Organization Test). EEG study is normal.

Patient starts a drug treatment with nimodipine (30 mg three times a day). After three months, tinnitus is considerably more frequent and severe. We change the treatment to Gabapentine (300 mg three times a day), but after one month it has to be interrupted because spatial disorientation and confusion. Tinnitus has not improved after this treatment. We decide to introduce the patient into our Tinnitus Retraining Therapy (directive counselling plus binaural white noise generators). A three month follow-up shows no changes in patient's own evaluation about the tinnitus, analogical scale score rises to 6 but THI improves to 16%. Patient is now more anxious, so we prescribe a benzodiazepine treatment (bromazepam 1.5 mg a day). After six months using white noise generators, the patient feels worse, THI increases to 64%, and intensity score remains on 6. Tinnitus is more frequent now, and it only improves mildly after a good 8 hours

sleep. Oscillopsia is not so disabling but it is perceived as frequent as its tinnitus. He still uses the generators but has lost the confidence in this treatment.

Discussion

These two cases present a common characteristic: changes in eye direction can evoke a subjective aural perception. While in case 1, gaze position is well defined (vertical eye direction), in the second case, patient refers changes in the environment as movements of the surrounding objects or a conflicting vision as the factor responsible for his tinnitus. After removal of a cerebellopontine tumour, it has been described several sensory perceptions evoked by gaze changes. Development of new connections between the auditory pathways and the neural centre for eye movements or the medial longitudinal fasciculus could be the explanation for this alteration in our first case [1,4,5].

In case two, we have not found any anatomical or physiological explanation for this phenomenon. The hypothesis of an interaction between cochlear pathways and brain areas for eye movement integration cannot be ruled out. On the other hand, the fact that vestibular testing shows a mild hypo-reflectivity on right labyrinth and dynamic posturography presents a minimal vestibular pattern could explain the aetiology as a vestibular peripheral alteration. Gaze changes related to confliction vision stimulus are the most probable tinnitus evoker factor in this patient. Head movement changes have not been related to the perception of the tinnitus nor the oscillopsia. Exploration and vestibular evaluation describes a peripheral vestibulopathy as the possible aetiology but we cannot rule out a central alteration in this case.

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Chronic tinnitus following electroconvulsive therapy

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Introduction: Tinnitus can be caused by almost any pathology involving the auditory system and can also result from head trauma, a variety of medications, and electrical shock including lightning strikes. This is the first published report of tinnitus that began immediately following electroconvulsive therapy (ECT).

Methods: A 43-year-old female with a 27-year history of obsessive-compulsive disorder and major depression had previously been treated with psychotherapy, antidepressant and antipsychotic medications. Because these treatments were minimally effective and because the frequency and duration of her depressive episodes continued to increase, the patient was scheduled to undergo a series of ECT procedures. The patient received four ECT treatments during one week. Stimulating current was delivered through a unilateral electrode to the right frontotemporal region of the head.

Results: EEG seizures occurred during each of the ECT procedures. After the patient recovered from anesthesia she complained of headaches, muscle pain, amnesia, and, after the fourth ECT, she reported a ringing sound in her right ear. Audiometric testing the day after the fourth ECT revealed a slight increase in threshold for 8000 Hz tones in her right ear.

Conclusions: It is likely that current delivered during the fourth ECT treatment triggered the perception of tinnitus for this patient. The unique organization of this patient's central nervous and auditory systems combined with her particular pharmacological history might have predisposed her to developing this symptom.

Introduction

Chronic tinnitus is experienced by millions of people throughout the world [1]. This symptom can result from almost any pathological condition affecting the auditory system including infections, hearing loss, cardiovascular disorders, metabolic disorders, or neoplasms [2]. Chronic tinnitus can also be caused by head trauma [3] and medications including quinine, salicylates, loop diuretics, aminoglycoside antibiotics, and some antineoplastic drugs [4]. The Physician's Desk Reference [5] lists dozens of medications that include tinnitus as a potential side effect. In most (but not all) cases, tinnitus resolves soon after patients stop taking the causative medication.

This paper describes the first published case of chronic tinnitus that began immediately after a patient received electroconvulsive therapy (ECT) for major depression and obsessive-compulsive disorder.

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Methods

The patient was a 43-year-old Caucasian female with a 27-year history of obsessive-compulsive disorder and major depression. Obsessiveness about her appearance began during her teen years when she experienced facial scarring from severe acne. In spite of ongoing treatment that included psychotherapy and at least eight different antidepressant medications (including several SSRIs and tricyclics), the frequency and duration of depressive episodes increased during the last ten years. After two recent suicide attempts, the patient was scheduled to receive a series of ECT treatments.

The patient underwent four separate ECT procedures during one week. ECT was administered according to the following parameters: Succinylcholine, glycopyrrolate, and methohexital were given intravenously prior to electrode placement. After the patient was under anesthesia, a unilateral electrode was placed on the right side of the scalp in the frontotemporal region. 0.9 Amps of stimulating current was delivered by a Thymatron ECT instrument (Somatomics Inc., Lake Bluff, Illinois) on a setting of 40% (224 total 1 msec bidirectional pulses were delivered over 2.24 sec).

Results

EEG seizures were elicited within 15 seconds after stimulus presentation during all four procedures (seizure duration ranged between 30–45 sec). After recovering from anesthesia following each procedure, the patient complained of headaches, muscle pain and amnesia. After the fourth ECT procedure she also reported hearing a high-pitched ringing sound in her right ear. The day after this procedure, she went to an otolaryngologist and was given a hearing test. Audiometric results (pure tone air conduction thresholds) from this test are shown in Figure 1. These results indicate essentially normal hearing with a slight increase in threshold at 8000 Hz for the right ear.

Six weeks after the fourth ECT procedure, the

patient was evaluated in our clinic. In addition to tinnitus and depression, the patient reported that she was also experiencing anorexia, excessive weight loss, and insomnia. She reported that she was taking clonazepam, quetiapine, and citalopram, but none of these medications was particularly effective. Pure tone air conduction thresholds recorded during this appointment are shown in Figure 2.

Compared to the audiogram recorded six weeks earlier, her thresholds at 6000 and 8000 Hz improved in both the left and right ears. However, the patient reported no noticeable reduction in tinnitus loudness. In fact, tinnitus was now perceived in both ears, but it was louder on the right side. She matched the sound of her tinnitus to a 4000 Hz tone at a loudness of 10 dB SL in the right ear and 5 dB

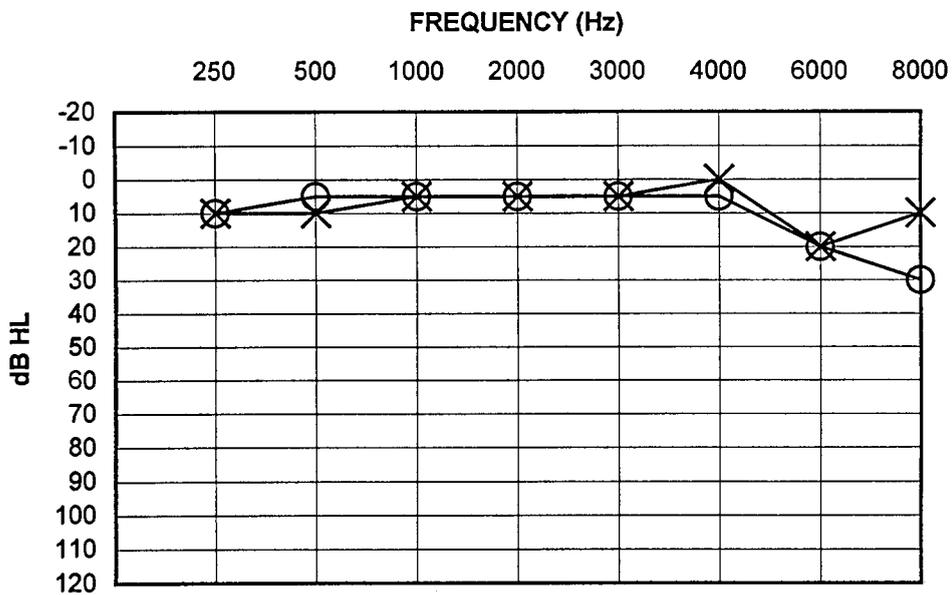


Figure 1 Audiometric thresholds one day after ECT

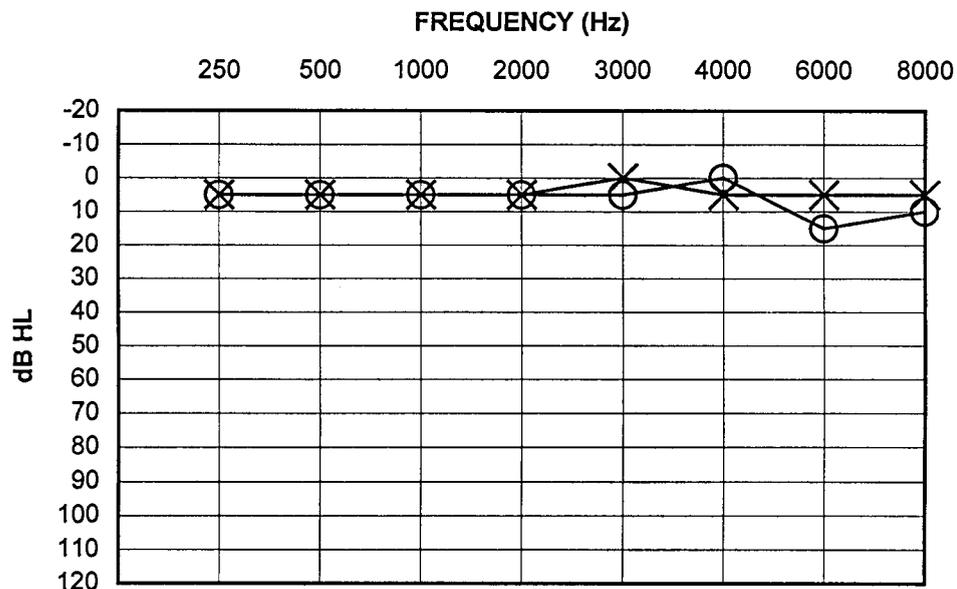


Figure 2 Audiometric thresholds six weeks after ECT

SL in the left ear. We made the following recommendations to her: (1) That she uses masking sounds to give her relief from tinnitus whenever possible. To facilitate this acoustic therapy, she purchased two ear level masking devices, a Sound Pillow (this pillow is embedded with two flat and flexible speakers that can be connected to any electronic sound producing device – the patient can then play any sort of pleasing or comforting music or sounds to help with sleep), and a CD with waterfall and nature sounds. (2) That she talks with her physicians about ways to improve her diet/appetite and to supplement her meals with multivitamins/minerals. (3) That she talks with her physicians about using alprazolam to reduce the loudness of her tinnitus. She was given a reprint of a study conducted in this clinic that used alprazolam for this purpose [6]. (4) That she talks with her physicians about alternative treatments for insomnia.

After leaving our clinic, the patient was transported to a psychiatric care facility for long-term evaluation and treatment. She continued to call our clinic on a regular basis (as she did before scheduling her appointment) to ask us if the tinnitus will ever stop. Our answer, which has always been unsatisfactory to this patient, was that we cannot say for sure, but the fact that her hearing recovered might be a positive indicator that her perception of tinnitus will eventually decrease. The acoustical therapy devices she purchased can facilitate this process.

Discussion

One could argue that this patient's tinnitus was caused by the medications that were used to prepare her for ECT. In fact, all of these medications have the potential for producing the side effect of tinnitus that is usually temporary. However, the patient did not experience tinnitus following the first three ECT procedures which used the same medications in the same dosages. Citalopram, clonazepam and quetiapine that the patient had been taking can also produce tinnitus. However, the patient had been taking these medications for several weeks or months prior to her fourth ECT and had not previously reported this side effect.

Because the patient reported that she heard tinnitus immediately after she recovered from anesthesia, it is likely that her fourth ECT procedure produced this symptom. We have seen at least six patients in our clinic who developed chronic tinnitus as a result of electrical shock. Several studies have reported tinnitus that resulted from lightning strikes [7–9].

The most common cause of tinnitus is damage to the cochlea that also results in hearing loss [2]. Shepherd *et al.* [10] demonstrated that electrical stimulation can cause degeneration of spiral ganglion cells within the cochlea. Three additional facts lend credence to the theory that ECT caused this patient's tinnitus to start: (1) The stimulating electrode was placed in the right temporal region of her scalp; (2) Audiometric testing of the patient the day

after her fourth ECT treatment showed reduced sensitivity for 8000 Hz tones in her right ear; (3) The patient originally perceived tinnitus in the right ear only. Even though the hearing in her right ear improved six weeks after the last ECT, the patient's perception of tinnitus remained constant. This observation is consistent with the model of tinnitus generation proposed by Lenarz *et al.* [11] who stated that "the induction of tinnitus usually involves pathologies of peripheral auditory structures" and "the manifestation and maintenance of tinnitus involves central auditory structures which are not necessarily impaired."

Why didn't this patient experience tinnitus after her first three ECT procedures? It is possible that these procedures were causing subtle changes to occur in peripheral or central auditory structures and that the fourth ECT was the trigger for tinnitus to begin. The fact that there are no other published reports of ECT causing the symptom of tinnitus indicates that it is a rare side effect. The unique organization of this patient's central nervous and auditory systems combined with her particular pharmacological history might have predisposed her to developing tinnitus.

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Is lamotrigine an effective treatment for tinnitus?

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Tinnitus is an extremely prevalent condition which at present, has no satisfactory clinical treatment. Development of therapy has been hampered by the diversity of underlying conditions which give rise to the symptom of tinnitus and therefore a drug which has multiple actions may have an improved chance of being effective. One such drug is lamotrigine, a recently developed anti-epileptic agent, which has both glutamate release inhibition and sodium channel antagonist properties.

Lamotrigine was evaluated in a double blind, placebo-controlled clinical trial. Patients were initially tested with an i.v. infusion of lignocaine (10 mg/ml) to a maximum of 100 mg or until a reduction in tinnitus was observed. Lamotrigine or placebo tablets were taken once daily (25 mg) for two weeks, 50 mg for two weeks and 100 mg for four weeks.

Patients were selected from amongst volunteers presenting at the local tinnitus clinic. Those whose tinnitus had been present for less than six months or whose tinnitus was likely to vary spontaneously were excluded. Perceived intensity and intrusiveness of tinnitus was assessed initially, and at 4 week intervals throughout the trial. Assessment comprised visual analogue scales, questionnaires, and a battery of audiological measurements.

Of the 31 participants who completed the trial, questionnaires indicated that lamotrigine was effective in a very few people. There was no correlation between the response to lignocaine and to lamotrigine. There was good agreement between the questionnaires and visual analogue scales in the reporting of perceived changes, however this was not reflected in changes in the audiological tests.

A preliminary report on this study was presented at the 5th International Tinnitus Seminar in Portland, Oregon.

Introduction

Despite being effective in approximately 60% of patients tested [1,2], lignocaine has no practical role in the treatment of tinnitus for the following reasons. The relief obtained is extremely short lived (3 minutes or less) and it is only effective when administered intravenously (i.v.). Relief may also be accompanied by undesirable side effects including confusion and dizziness [3]. Endeavours to capitalise on lignocaine's effectiveness, have as yet, proved fruitless. It is unlikely that sodium channel blocking activity is the only mechanism by which it brings relief, as neither lignocaine's orally active analogues (e.g. tocainide), nor other sodium channel blockers (e.g. phenytoin), have been found to be effective [3–7]. Attempts to extend the period of relief and to administer it by different routes have been unsuccessful,

as direct intra-tympanic instillation often causes unacceptable vertigo and nausea. It may be that a large bolus of lignocaine is necessary for tinnitolytic and that this is unattainable via the oral route. However, the very fact that there is such an effective pharmacological agent has maintained the hope for development of an effective and accessible treatment.

Lamotrigine has several pharmacological characteristics in common with lignocaine. Both drugs block sodium channels, however, lamotrigine acts on only a specific subset of the channels [8]. In *in vitro* experiments, blockade of these channels inhibits the release of glutamate and since only 'activated' channels are affected, basal glutamate release is unaffected [9,10]. This could explain why there is no general depression of function when it is given as an anti-epileptic [9]. There is strong evidence to suggest that glutamate plays an important role at both peripheral and central levels in the auditory system, and therefore glutamate function may be involved in tinnitus generation, its perception, or both. As lamotrigine and lignocaine can both cross

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the blood brain barrier, they can also access the cochlea and hence, be active at either or both sites. Any number of different conditions can give rise to the perception of tinnitus and so it seems likely that a drug which has multiple actions, or which is active centrally and peripherally has the greatest chance of being effective in a broad population of tinnitus patients. According to the manufacturer's data, lamotrigine fulfils the criteria for an 'ideal' anti-epileptic drug [11] and several of these criteria also make it extremely practical as a prospective treatment for tinnitus. Lamotrigine can be given orally once a day, it has reliable absorption and metabolism characteristics [12], it is unlikely to interact with other medications being taken and has few side effects. Its clinical suitability is evidenced by its increasing use as an anti-epileptic agent, particularly in the treatment of epilepsy characterised by multiple seizure patterns [13].

Lignocaine 'screening' has been used to try and predict the effectiveness of other drugs (most commonly carbamazepine) with variable results [14,15]. This variability may arise because lignocaine has a number of potential 'target' sites and it is still a matter of debate whether lignocaine acts primarily in the periphery or centrally. Some experimental evidence points towards an action in the CNS. This includes recent PET scan data, clearly indicating a measurable central effect, coincident with attenuated tinnitus [16]. There has also been some dispute as to the effectiveness of lignocaine when applied by intra-tympanic injection. Podoshin *et al.* [17] found it to be effective, whilst Coles *et al.* [18] did not. Further evidence exists which indicates a peripheral site. For example, lignocaine has been shown to be particularly effective in tinnitus accompanying Ménière's syndrome, a pathological condition localised in the cochlea and vestibular apparatus [19–21]. Lignocaine has also been shown to decrease the compound action potential (CAP) [22], and the distortion product otoacoustic emission (DPOAE) in humans [23,24]. Elucidation of lignocaine's site and mode of action may be crucially important in the development of pharmacological tinnitolytic agents. Indeed, Jackson [19] suggests that if lignocaine can be proven to act peripherally then there is no point in pursuing the actions of centrally acting drugs like the anti-epileptics.

Methods

Patients (between 18–75 years of age) were taken from a general tinnitus clinic population without pre-selection for underlying pathologies or hearing deficits. Exclusion criteria were intended primarily to exclude anyone whose health could be adversely affected by taking part in the trial (pregnant females, those in poor general health, any history of gastro-intestinal, hepatic or renal insufficiency or treatment for epilepsy). A secondary criterion for exclusion from the trial was the existence of spon-

taneous fluctuations in the tinnitus as these would affect the reproducibility of the assessments of tinnitus discomfort or intrusiveness.

Prior to the commencement of treatment, patients were given a slow intravenous infusion of lignocaine (1%), administered until the patient reported a significant change in the intensity or nature of their tinnitus, or up to a maximum dose of 100 mg. In an attempt to establish whether tinnitolytic doses of lignocaine coincided with a measurable effect on the central nervous system, patients were tested for short-term memory, attention and central processing by three different tests performed immediately before and after completion of the infusion. Short term memory was evaluated by recording the number of digits that could be remembered after recitation forwards and backwards. The time taken to complete trail tests (alternating numbers and letters) were also recorded. A pre-trial questionnaire established time of onset, degree of intrusiveness, general history and factors which were perceived to influence the tinnitus.

Trial design

The trial was double-blinded, placebo-controlled, crossover, lasting 16 weeks in total. Patients (31) were randomly allocated to drug or matching placebo tablets for the eight weeks before cross-over. There was no washout period between the first and second phases.

Assessment

Tinnitus was assessed on 5 separate occasions, at 0 weeks, 4 weeks, 8 weeks, 12 weeks and 16 weeks. Table 1 shows the audiological measurements which were made. These are the minimum requisites for the assessment of tinnitus in trials of potential treatments for the condition (as outlined by Axelsson *et al.* [25]). The subjective assessment included 100 mm long visual analogue scales on which subjects were instructed to mark a position which represented their present loudness, annoyance and awareness. Subjects also answered 4 questionnaires which asked 'has your tinnitus changed?' with possible responses of ; 'slightly better', 'much better', 'slightly worse', 'much worse' or 'no change' (indicated in diagram 1).

Tables 1 Audiological measurements

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- (a) Pure tone audiometry to establish air conduction thresholds.
 - (b) Masking audiogram (using narrow band noise).
 - (c) Pitch matching of most troublesome tinnitus (MTT) by forced choice discrimination.
 - (d) Loudness matching of MTT at pitch matched frequency (PMF) and 1000Hz.
 - (e) Narrow band masking of MTT.
 - (f) Residual inhibition.
 - (g) Uncomfortable loudness levels at PMF and 1000Hz.
-

Diagram 1 Effect of treatment on tinnitus, assessed by questionnaire.

| Report | | Response | | | | | total |
|---------|--------------|------------|----------|-----------|----------|-------------|-----------|
| | | much worse | worse | no change | better | much better | |
| Placebo | much worse | 0 | 0 | 0 | 0 | 0 | 0 |
| | worse | 0 | 0 | 1 | 1 | 0 | 2 |
| | no change | 0 | 3 | 13 | 7 | 0 | 23 |
| | better | 0 | 0 | 3 | 0 | 3 | 6 |
| | much better | 0 | 0 | 0 | 0 | 0 | 0 |
| | total | 0 | 3 | 17 | 8 | 3 | 31 |

Notes: The effect of treatment as assessed by questionnaire. The questionnaire responses for placebo and lamotrigine were compared for each subject and the tablet that received the most positive response was denoted to be the tablet of preference. Using this method, lamotrigine was preferred by 12 of the 31 subjects. The data show a strong placebo effect, but subjects are significantly more likely to report a response to lamotrigine treatment than to placebo (Chi square $p < 0.05$). No correlation was observed between the response to lignocaine and lamotrigine. Lamotrigine tablets were significantly ($P < 0.05$) more likely than placebo, to be chosen as the tablet of preference, when assessed by questionnaire. Analysis of the questionnaire responses shows that of those six subjects who preferred placebo, three had reported a negative response to lamotrigine. All three of the 'much better' reports were in response to lamotrigine, however, these subjects also reported a positive 'better' response to placebo.

Results

Of the 33 patients who entered the trial, 31 completed (19 males, 53 ± 3 years; 12 females, 58 ± 3 years). Two subjects withdrew, one on placebo reporting dizziness and rash, the other, taking lamotrigine reported nausea, vomiting and headache.

None of the tests showed significant differences for 'before' and 'after' values and therefore there is no detectable effect on central function (despite almost two thirds of subjects reporting a significant reduction in tinnitus). The slight (but not signifi-

cant) improvement in times for trail tests 'after' is probably due to a learning effect.

This shows the average loudness matches (\pm s.e.m) using pure tones at the PMF and at 1 kHz and narrow band noise (NBN) centred on the PMF. The matches with pure tones at PMF are consistently louder than at 1 kHz or with the narrow band noise (NBN). The matches show no significant changes after either lamotrigine or placebo, compared with visit 1 matches, even when divided into groups by tablet preference. Values for the group who 'prefer neither' are extremely stable and are consistently higher than for other groups. The average loudness matches at 0.5/1 kHz are significantly ($p < 0.05$) lower than those performed at the PMF for all of the groups.

Table 2 Responses from the psychometric tests performed before and after lignocaine testing

| | | Response to lignocaine | |
|-----------------------|--------|------------------------|---------------|
| | | Positive | No response |
| No of subjects | | 20 (64.5%) | 11 (35.5%) |
| Trail test(s) | Before | 100 \pm 12 | 107 \pm 13 |
| | After | 96 \pm 9 | 95 \pm 10 |
| "Forward" digit span | Before | 5.7 \pm 0.2 | 5.7 \pm 0.2 |
| | After | 5.4 \pm 0.2 | 5.4 \pm 0.2 |
| "Backward" digit span | Before | 3.4 \pm 0.2 | 3.5 \pm 0.3 |
| | After | 3.5 \pm 0.2 | 3.0 \pm 0.2 |

Notes: There was no significant difference in the test responses between 'positive' and 'no response' groups before and after lignocaine infusion.

Discussion

The questionnaire responses gave the strongest indication of lamotrigine's tinnitolytic potential, however, these positive reports were not reflected in the values obtained in the audiological tests. The most probable reason for this is the widely reported variability in the audiology and difficulties in interpretation of these measures. It could be argued that, in the absence of objective measurements, the patients reported perception of tinnitus is the most important indicator of any change in the condition. Since there is no clear correlation between measurable audiological parameters and the distress caused by the condition, well validated 'Quality of life' type questionnaires (e.g. the Tinnitus handicap

Table 3 Visual analogue scale (VAS) scores (mm) subdivided by tablet preference

| Time of test | Tablet preference | VAS scores | | |
|-------------------|-------------------|-------------|-------------|-------------|
| | | Loudness | Annoyance | Awareness |
| Visit 1 | All subjects | 52.8 ± 4.8 | 51.6 ± 5.4 | 63.3 ± 5.3 |
| | Neither | 68.5 ± 6.5 | 71.4 ± 5.6 | 73.2 ± 5.7 |
| | Placebo | 43.8 ± 8.6 | 31.5 ± 8.2 | 52.7 ± 14.3 |
| | Lamotrigine | 40.4 ± 7.1 | 40.3 ± 9.3 | 57.8 ± 9.7 |
| After placebo | All subjects | 58.5 ± 4.8 | 56.3 ± 4.8 | 63.9 ± 5.3 |
| | Neither | 70.1 ± 7.5 | 64.2 ± 7.4 | 69.6 ± 8.0 |
| | Placebo | 52.0 ± 7.6 | 45.0 ± 8.6 | 60.5 ± 9.8 |
| | Lamotrigine | 49.1 ± 7.9 | 53.3 ± 8.5 | 59.5 ± 9.7 |
| After lamotrigine | All subjects | 60.8 ± 4.4 | 60.1 ± 4.6 | 65.8 ± 4.7 |
| | Neither | 69.0 ± 5.9 | 68.9 ± 6.0 | 69.8 ± 7.0 |
| | Placebo | 56.2 ± 11.6 | 57.7 ± 11.4 | 65.5 ± 10.8 |
| | Lamotrigine | 54.2 ± 7.2 | 51.8 ± 7.7 | 61.7 ± 8.3 |

Notes: The values for all of the parameters at visits 1, 3 and 5 are shown. The values for 'all' subjects do not change significantly after either tablet, and even when the groups are subdivided by their expressed tablet preference, the VAS scores show no significant improvement following their tablet of preference.

Table 4 Loudness matching (dB) for subjects, subdivided by tablet preference

| Time of test | Tablet preference | Loudness matching | | |
|-------------------|-------------------|-------------------|-----------|-----------|
| | | Loudness | Annoyance | Awareness |
| Visit 1 | All subjects | 60 ± 4.4 | 35 ± 4.8 | 47 ± 4.3 |
| | Neither | 69 ± 5.6 | 40 ± 6.4 | 54 ± 4.3 |
| | Placebo | 57 ± 7.9 | 28 ± 4.0 | 45 ± 6.2 |
| | Lamotrigine | 49 ± 8.2 | 27 ± 8.7 | 35 ± 8.4 |
| After placebo | All subjects | 62 ± 4.8 | 39 ± 4.6 | 49 ± 4.5 |
| | Neither | 70 ± 5.6 | 40 ± 4.9 | 58 ± 5.8 |
| | Placebo | 65 ± 12 | 38 ± 8.0 | 52 ± 10 |
| | Lamotrigine | 47 ± 9.2 | 34 ± 10 | 36 ± 8.7 |
| After lamotrigine | All subjects | 61 ± 5.3 | 36 ± 4.2 | 48 ± 4.9 |
| | Neither | 69 ± 5.5 | 40 ± 5.0 | 56 ± 5.0 |
| | Placebo | 63 ± 9.7 | 36 ± 2.4 | 48 ± 10 |
| | Lamotrigine | 56 ± 11.0 | 38 ± 9.7 | 43 ± 9.0 |

inventory) may be the best means of evaluating prospective remedies [26,27].

The responses to lignocaine were in accordance with the findings of other workers – almost complete relief for approximately 50% of sufferers and partial (but significant) relief for an additional 25% [22]. The psychometric tests did not indicate deficits in central function, co-incident with tinnitolytic doses of lignocaine. This could indicate that lignocaine's tinnitolytic properties are independent of its established central effects [16]. However, despite the lack of evidence from the tests, it was apparent that the subjects were suffering some confusion, possibly indicating that lignocaine can indeed influence central processes without influencing the psychometric tests used here. Since there is evidence supporting activity at both peripheral and central sites, it is possible that lignocaine's activity at both contributes towards the tinnitolytic effect. The contribution made by each site may vary depending on the particular pathology present and this could go some way towards explaining the

ambiguous findings of the numerous studies made of lignocaine.

The results from this small trial do not indicate a significant positive response to lamotrigine as a treatment for tinnitus. However, there were a number of people who reported considerable relief and this may suggest that there is a sub group of sufferers (perhaps defined by underlying pathology or duration of tinnitus experience) who could be successfully treated with lamotrigine. A larger trial would be needed to pinpoint the factors which characterise any potential subgroup (as discussed by Møller in the commentary on the baclofen trial [28]). Numerous attempts have been made to identify characteristics by which tinnitus patients can be reliably subdivided as potential groupings for therapy. In one such effort, Feldmann [29] identified a number of distinct masking curve patterns by which most sufferers could be categorised, however, this has proven to be of limited clinical use. More recently, late auditory (cortical) evoked responses have been investigated to determine whether there

are differences in the way that tinnitus sufferer's process auditory information [30]. It was found that the sufferer's responses could be grouped according to how their tinnitus was influenced by noise. These differences may give clues as to the mechanisms by which tinnitus perception arises and therefore indicate the likelihood of susceptibility to particular therapies. Our attempt to group subjects according to lignocaine response was not found to be an effective pre-selection tool in this trial.

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Ginkgo – more fact than fiction!

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Positive effects of the extract of Ginkgo Biloba (EGB) have been monitored for the last ten years by 630 participants of the Baltimore Area Tinnitus Self-Help Group.

Introduction

It all began in 1987. Your author came home from the Third International Tinnitus Seminar in Muenster, Germany armed with positive literature regarding the effects of the extract of Ginkgo Biloba (EGB) on tinnitus [1]. The Chinese, French and Germans had been using it for years and reported several double-blind placebo-controlled studies. The articles, however, were difficult and sometimes impossible to translate. The over-all consensus of opinion for dosage appeared to be 120 mg per day. Our Baltimore Area Tinnitus Self-Help Group debated its support. A visiting otolaryngologist raved about its success with his allergy patients who reported tinnitus. A member-pharmacist/nutritionist investigated and suggested a phytosome form of EGB to insure the most nutritional benefit.

The phytosome process reportedly obtains the highest value from herbal extracts by intensifying the power of standardized herbs assuring improved activity and enhancing delivery of the nutrients to cell membranes [2]. Our member pharmacist feels that EGB phytosome is superior in purity and strength. It contains no sugar, salt, yeast, wheat, corn, dairy products, coloring, flavoring or preservatives. EGB phytosome is a complex of phosphatidylcholine and standardized extract of EGB containing 24% ginkgoheterosides. Phytosome is a bonding agent, not an additive.

So we took the plunge. We started informally and by March, 1991, began keeping records with 52 members reporting positive results. By 1995 we had over 200 in our EGB project and developed a survey/questionnaire form. By 1998 we had 512 in our project and this final summary presentation for the VIth International Tinnitus Seminar concludes with 630 participants.

It is thought that the Ginkgo is the world's oldest living species of tree [3]. Also known as the Maiden-hair tree, Ginkgo was thriving during the age of the

dinosaurs, some 250 million years ago. Its leaves are fan-shaped, smooth and tough, and about four inches long, turning from green to yellow in the fall. The trees themselves grow to about 100 feet high, bear an inedible fruit and live as long as 1,000 years or more. It is the leaves, which have proven to possess health-enhancing qualities. The Ginkgo leaf extract has been used in Chinese medicine for at least 5,000 years [4]. The Ginkgo tree is remarkably resilient to insects, disease and pollution, which accounts for its survival through the ages and today is a popular addition to major boulevards streets and parks. Plantations now flourish in the Far East where Ginkgo trees are specifically grown for pharmaceutical purposes. A link has been discovered between the tree's survival and the health secrets man has uncovered from its leaves.

Tried and tested methods of extracting the magic of the Ginkgo tree have been used for centuries. Today's techniques offer sophisticated chemical analysis and biomedical specialists can identify and track the benefits to the human body. The leaves are harvested in the fall as they turn from green to yellow. They are dried in hot-houses that are temperature controlled and then separated from any foreign matter such as twigs or stalks that might interfere with the final extract. They are then pressed into bales, kept under constant temperature and humidity and shipped off to an extraction plant. There the leaves are pulverized and repeatedly mixed with organic solvents, which liberate the chemical components of the leaves. The crude extract is then further refined to a point where the flavonoids make up a precise 24% concentration of the mixture [5]. This is the proven therapeutic optimum effect used by many countries.

In several studies the beneficial effects experienced from EGB are remarkable [6]. It appears to improve circulation, metabolism, blood viscosity and neurotransmission in the aging. Improvements with EGB seem to come from an increased cerebral blood flow and therefore oxygen and glucose utilization. EGB also tends to increase the rate at which

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information is transmitted at the nerve cell level. There have been observable improvements in mental performance, muscular rehabilitation, early senility, macular degeneration, sensorineural hearing loss, edema, and of most importance to us – tinnitus and hyperacusis [7].

Methods

Our survey/questionnaire was made available to all whom were members of our Baltimore Area Tinnitus Self-Help Group or who desired to be a part of our on-going project. We have followed the universally suggested dosage of 40 milligrams three times a day with food and have found that it should be taken consistently for at least twelve weeks to determine its effectiveness. All participants took their EGB for at least three months before completing their first questionnaire, which determined this effectiveness. It seems the longer the EGB treatment continues the more obvious and lasting the results. At least eight days generally seem necessary before the first effects are manifested.

Only twelve dropped out of our project within the first two weeks of taking EGB. Reasons included upset stomach, dizziness, headaches, and a feeling that the tinnitus had worsened. These twelve are not included in our total number of 630.

Results

In addition to some generalities, we have evaluated four specific questions from our survey/questionnaire. Generally, we are gender specific with 427 men and 203 women. Our ages as we began taking EGB range from 18–82. Of our total final number of 630, the average length of time for taking EGB is three years.

The four specific questions involved a rating scale of 1–10 with 10 being the worst (N = 630).

The first question asked the participant to rate the following symptoms on a scale of 1–10 before taking EGB:

| | |
|--------------------------|---------|
| | Average |
| Rating: Tinnitus/ringing | 7 |
| Dizziness/unsteadiness | 1 |
| Hearing loss | 3 |
| Fullness/pressure | 1 |

The second question asked the participants to rate the same symptoms at the time they completed their questionnaire:

| | |
|--------------------------|---------|
| | Average |
| Rating: Tinnitus/ringing | 5 |
| Dizziness/unsteadiness | 1 |
| Hearing loss | 3 |
| Fullness/pressure | 1 |

The third question asked the participants to evaluate their quality of life before taking EGB using the same scale of 1–10 with 10 being the worst:

Average
6

Rating:

The fourth question asked the participants to evaluate their quality of life at the time they completed the questionnaire using the same 1–10 scale.

Average
6

Rating:

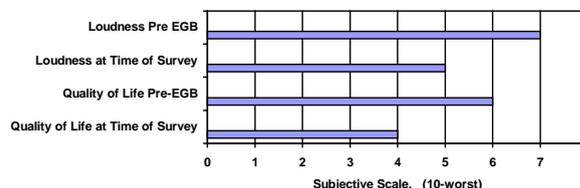


Figure 1 Average rating of tinnitus and quality of life before taking EGB and at the time of our survey (N = 630).

Conclusions

Of our 630 who continue to take EGB, we feel that the average 2 point reduction in tinnitus and 2 point increase in the quality of life is beneficial. No one’s tinnitus has disappeared, but we believe any improvement is subjectively significant.

In addition, participants were asked to comment on other positive experiences from their EGB. The 18 who reported hyperacusis noted that it had improved for them. There were 6 who reported they and their physicians believed their macular degeneration had been in remission since they began taking EGB. Other positive improvements include a general feeling of well being, improved energy, lower blood pressure, better appetite, and better sleeping with less fatigue.

We have investigated reports of EGB interfering with blood-clotting ability [8,9]. We caution those taking any blood thinners such as Coumadin to thoroughly discuss their participation in our project with their physician before proceeding. We also caution its use with any aspirin medications. We understand when drugs, including vitamins and herbs, are incompatible their actions are altered [10]. Complications can be highly toxic [11]. Blood studies are recommended to test for the length of time for blood coagulation.

Initially, in 1990, we wondered if our improvements were more fiction than fact. We pose the same question now as we did then [12]. Is our tinnitus and hyperacusis improved because we feel better and are dealing more positively with these symptoms? We believe the validity of our EGB project is enhanced by this increased participation. We who remain are committed to our daily dose of EGB and sharing our ongoing progress. We believe our improvements are more fact than fiction!

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Does lignocaine interact with serotonin (5-HT) function?

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Many anecdotal reports and several well-controlled trials have clearly shown that intra-venously administered lignocaine is effective in some 60 or 70% of tinnitus patients. Despite our comprehensive knowledge of the mode of action of lignocaine when acting as a local anaesthetic or an anti-arrhythmic, we have no evidence to suggest that it is via sodium channel blockade that it is effective in tinnitus. On the contrary, the virtual ineffectiveness of other sodium channel antagonists would suggest that we have yet to identify the mechanism by which lignocaine attenuates tinnitus.

As lignocaine has a very short half-life when administered intravenously and has some troublesome side effects, its use as a tinnitolytic agent has been more or less limited to that of an experimental tool. Nevertheless, the fact that it is the most reliable pharmacological means of alleviating tinnitus, indicates that elucidation of its mode of "tinnitolysis" should be a great step forward in the development of an effective pharmaceutical agent for the treatment of tinnitus.

From a comparison of the structure of lignocaine and endogenous neurotransmitters, it can be seen that lignocaine and some of its metabolites are structurally similar to serotonin (5-HT). Furthermore, there are other correlations that can be made between tinnitus and serotonin e.g. lignocaine is effective in both tinnitus and in migraine, (and serotonin active drugs are the mainstay of migrainetherapy). In addition, many tinnitus patients claim that their tinnitus is at its worst when they awaken and the state of wakefulness is largely under the control of serotonin. Serotonin is also widely distributed within the central parts of the auditory system and auditory frequency discrimination has also been extensively used to monitor the potency of serotonin drugs.

We have used various physiological systems unrelated to audition to assess the interaction between lignocaine and the different types of serotonin receptors. We report on the effectiveness of lignocaine in attenuating the response to serotonin in some of these systems.

Introduction

The fact that lignocaine's classical local anaesthetic action, seems unlikely to be the sole or even major route by which it has its tinnitolytic effect, has led to much investigation into other mechanisms by which it may be effective. It is improbable that the widespread blockade of sodium channels and resulting central nervous system depression is responsible for the effect, as other local anaesthetics are ineffective. Lignocaine may somehow attenuate the tinnitus signal or its perception, by altering activity of the neurotransmitter or transmitters which maintain the signal. A comparison of lignocaine's structure with neurotransmitters shows marked structural similarity between lignocaine and 5-HT (5 hydroxytryptamine) or serotonin.

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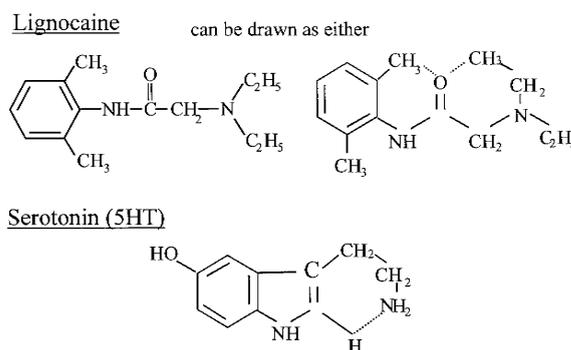


Figure 1

5-HT (serotonin), was first isolated in serum by Rapport in 1948, reportedly has 14 different mammalian receptors and these are further grouped into 7 families, according to their structure and pharmacology. 5-HT receptors are widely distributed and its pathways are crucial to a number of functions, including control of mood and emotion, modulation of sensory pathways, perception of hallucin-

ations, nociception and control of sleep/wakefulness.

5-HT in auditory pathways

There is much evidence to support a major role for 5-HT at a number of different levels in central auditory processing. Experimental data has localised serotonergic fibres and terminal endings in all of the auditory nuclei (cochlear nucleus – CN, inferior colliculus – IC, superior olivary complex and the nuclei of the lateral lemniscus) [1]. 5-HT_{1A} receptors have been identified in the CN and IC [1], and dense 5-HT₂ and 5-HT_{1A} binding has also been demonstrated in the primary auditory area [2]. Ionophoretically applied 5-HT has been shown to influence CN neurones by either facilitating or inhibiting activity in response to inputs from other neurones [3]. This mediation allows 5-HT to shape or filter the output from neurones making it a major mediator in auditory information processing.

The actual 5-HT cell bodies are not generally found in the auditory nuclei, and it seems likely that the network of 5-HT_{1A} innervation performs a predominantly modulatory role in the processing of sound [1]. The mechanism for this modulation may be through a process of “self” or autoregulation of 5-HT, similar to that which occurs in the serotonergic caudal raphe neurones. These receive glutamatergic inputs which can be inhibited by activation of pre synaptic 5-HT_{1B} receptors. Hence, activation of the neurone releasing 5-HT could act via pre synaptic 5-HT_{1B} receptors on the glutamatergic inputs to the neurone [4]. Auditory input from the CN may also modulate the activity of serotonergic and adrenergic cells elsewhere in the CNS thus inducing adaptation [5]. These processes form part of the mechanism by which 5-HT could facilitate the crucial process of habituation to auditory stimuli.

Surgical or pharmacological interruption of 5HT_{1A} pathways of the raphe nuclei results in exaggerated responses to sensory stimuli, causing animals to be easily startled and responsive to stimuli which would not normally elicit an effect. Disruption of some of these pathways has also been shown to impair inhibitory associative learning [6] indicating that the normal ability to disregard irrelevant forms of sensory input requires intact 5-HT pathways. In general, electrophysiological evidence shows that 5-HT acts mainly in an inhibitory role. It is therefore a relatively small step to the hypothesis that a fault in this mechanism (through disrupted 5-HT function), could lead to loss of filtering and the lack of habituation to tinnitus.

Tinnitus perception may be influenced by other processes in which 5-HT plays a modulatory role. Activation of 5-HT_{1A} and 5-HT₂ receptors shapes neural activity in the IC and hence modifies “defensive” behaviour [7]. Similarly, 5-HT’s influence on the CN may be intimately related to the level of arousal or behavioural state, as much of the CN’s 5-HT arises in the superior raphe nuclei. These

fibres also project to basal ganglia and limbic structures (which control the response to stressful stimuli) [8]. Stress is perhaps the most commonly reported factor when tinnitus sufferers are asked what exacerbates their tinnitus and it may be that an interaction between these areas controlling stress responses and auditory nuclei (via serotonergic transmission) is responsible.

5-HT and pathological conditions

Abnormal function in serotonergic systems is implicated in a number of clinically important conditions. These include schizophrenia, depression, sleep disorders and migraine and there are aspects of these conditions which show marked similarities to tinnitus. Depression is a very common accompaniment to tinnitus, and researchers have attempted to identify whether certain personality traits link or pre-dispose people to either condition [9]. Phonophobia, aural fullness and ear pain are common accompaniments of both migraine and tinnitus. In migraine, these symptoms appear to be centrally mediated and can be treated with drugs [10]. 5-HT is the neurotransmitter involved in induction and maintenance of sleep [11] and alteration in its function may explain why tinnitus is often reported to be at its worst after waking from sleep.

Tinnitus is often compared to the sensation of chronic pain [12] and in particular, phantom limb pain (PLP). Measurable plastic reorganisation in the cortex has recently been shown to accompany PLP [13] and correspondingly, salicylate-induced tinnitus correlates with plastic changes in auditory nuclei [14] and it has been deduced that salicylate-induced tinnitus is associated with changes in CNS processing of sound [15]. PET (positron emission tomography) studies of tinnitus sufferers have shown both increases in metabolic activity in Brodmann area 41 (the primary auditory area) [16] and unusual activity in the limbic system attributed to “aberrant” links [17], when compared with normal controls. As with PLP, this unusual activity has been attributed to plastic changes in response to peripheral de-afferentation. Dense 5-HT₂ and 5-HT_{1A} binding has been shown in Brodmann areas 41–42 [18] and PET has shown that 5-HT_{1A} receptors are particularly concentrated in the limbic system [19]. Therefore, a link between abnormal 5-HT activity in the CNS and tinnitus is credible.

Lignocaine and 5-HT

There are various pieces of experimental evidence indicating an interaction between 5-HT and lignocaine. The interaction may be at receptor level (through binding to one or more 5-HT receptor subtypes), or in a non-receptor mediated mechanism on 5-HT, by influencing storage, release, uptake or synthesis.

Large doses of lignocaine cause a clinical syndrome characterised by a number of symptoms

including psychosis, headache, visual and auditory disturbances. Heightened levels of anxiety appear to render people more susceptible to this [20] and it is suggested that these effects are mediated by the limbic system perhaps via an interference with 5-HTergic inhibitory pathways [21]. Very large doses of lignocaine will cause convulsions and this too, has been linked to 5-HT function [22, 23, 24]. Agents that suppress serotonergic transmission were found to increase the incidence of lidocaine-induced convulsions, whereas drugs that facilitate serotonin function decreased the susceptibility [22]. Depletion of noradrenaline and dopamine were found to have no effect on seizure threshold [23]. Experiments have shown that so-called "short sleep mice", which have low CNS 5-HT levels, are more prone to lignocaine convulsions [25]. This could be interpreted as supporting the hypothesis that 5-HT (and perhaps dopamine) maintains an inhibitory mechanism and lignocaine "inhibits" this inhibition, giving rise to convulsions [24].

Perhaps the most persuasive evidence of a link between 5-HT function and lignocaine is provided by studies of auditory evoked potentials (AEPs) (corticals and brainstems). Late (or cortical) potentials have been used as a surrogate marker of central 5-HT function [26,27] and it has been shown that potentials measured in individuals who suffer from the conditions of migraine and schizophrenia have characteristic abnormalities in their responses. In migraine, this takes the form of abnormally high intensity dependence of auditory evoked potentials which has been attributed to low serotonergic transmission [28]. In schizophrenia, the mechanism of "inhibitory gating" which reduces responses to repeated auditory stimuli appears to be compromised [29]. Modern pharmaceutical migraine treatments with 5-HT active agents have been shown to decrease the intensity dependence of AEPs [30]. A recent clinical study of AEPs in tinnitus sufferers has hypothesised a link between the perception of tinnitus and altered central 5-HT function [31].

A number of investigators have detected changes in the auditory evoked response of people when their tinnitus is ameliorated by lignocaine [32,33,34]. Others have been unable to detect such changes and therefore the evidence of a link between lignocaine and 5-HT, as indicated by evoked potentials, is still equivocal.

Methods

The aim of the study was to assess whether there was a measurable interaction between lignocaine hydrochloride and 5-HT function or receptors. The affinity of lignocaine hydrochloride for human serotonergic receptors was assessed in radioligand binding assays. The concentration of lignocaine which was required to produce tinnitolytic [35] was used as one of the points in binding assays.

Ileum experiments

Guinea pig ileum preparations were used to characterise the response to 5-HT and to investigate whether lignocaine influenced the 5-HT response in a way other than through sodium channel blockade.

Binding assays

The assays were performed (by CEREP) using the following general methods. Lignocaine hydrochloride was tested in each assay at 10 μ m and 75 μ m in duplicate. In each experiment, the respective reference compound was tested at a minimum of eight concentrations in duplicate to obtain a competition curve. The specific radioligand binding to the receptors is defined as the difference between total binding and non-specific binding determined in the presence of an excess of unlabelled ligand.

Following incubation, the membranes were rapidly filtered under vacuum through glass fibre filters. The filters were then washed several times with an ice-cold buffer using a cell harvester. Bound radioactivity was measured with a scintillation counter using a liquid scintillation cocktail.

Ileum preparation

Ileum was removed, cleaned and treated in the usual manner. The tissue remained viable for up to three days when stored on ice, in gassed (95% O₂/5% CO₂) Tyrode's buffer. The preparation was used in the standard/classical manner, with 1–2cm lengths of ileum suspended in warmed, gassed Tyrodes solution in an organ bath. One end of the ileum was attached to a fixed point at the bottom of the bath and the other was attached through a lever, to an isotonic transducer. The contraction was recorded on a pen recorder and was translated into "percentage of maximal contraction". Drugs (lignocaine, 5-HT and acetylcholine) were freshly

prepared in Tyrodes and stored on ice for each experiment. Each was introduced into the organ bath in measured doses, the response recorded and the bath washed out. The cycle allowed two minutes between each injection of 5-HT in order to avoid tissue fatigue and attenuated responses. Lignocaine was injected 1–2 minutes prior to agonist (Ach or 5-HT) injection.

Results

Binding assays

Results are expressed as a percentage of control specific binding and as a percentage inhibition of control specific binding obtained in the presence of lignocaine HCl. IC₅₀ values (the concentration which causes half-maximal inhibition of control specific binding) and Hill coefficients (nH) were for

Table 1

| Receptor | Tissue | Ligand | Non-specific | Incubation |
|------------------------|-----------------------------------|---|-----------------------|--------------|
| 5-HT _{1A} | human recombinant (CHO cells) | [³ H]-OH-DPAT (0.3 nM) | 8-OH-DPAT (10 µM) | 60 min/22°C |
| 5-HT _{2A} | human recombinant (CHO cells) | [³ H]ketanserin (2 nM) | Ketanserin (1 µM) | 15 min/37°C |
| 5-HT _{2C} | human recombinant (CHO cells) | [³ H] mesulergine (0.7 nM) | Mesulergine (1 µM) | 30 min/37°C |
| 5-HT ₆ | human recombinant (HEK 293 cells) | [³ H]LSD (2 nM) | Serotonin (100 µM) | 60 min/37°C |
| 5-HT ₇ | human recombinant (HEK 293 cells) | [³ H]LSD (4 nM) | Serotonin (10 µM) | 120 min/22°C |
| 5-HT _{uptake} | human recombinant (HEK 293 cells) | [³ H]paroxetine (0.1 nM) | Imipramine (10 µM) | 30 min/22°C |

the reference compounds by non-linear regression analysis of their competition curves. These parameters were obtained by Hill equation curve fitting.

Ileum experiments

Contraction of the ileum preparation in response to either 5-HT or acetylcholine (ACh) was measured and standard responses were noted. Lignocaine was added to the bathing solution in order to test whether there were measurable changes in the effects of either ACh or 5-HT on the ileum. Preliminary data indicated that lignocaine (8.3×10^{-6} – 1.82×10^{-5} M) did not cause significant decreases in response to any dose of acetylcholine, however, under the same conditions, the identical doses of lignocaine were found to attenuate responses to 5-HT.

Ileum is reported to remain viable for up to three days if stored carefully under the conditions described above. Contractile responses to acetylcholine were found to remain stable across all three

days of experimentation, however, it was found that increasing doses of 5-HT were necessary to evoke the same size of response. It was also noted that the lignocaine's attenuation of responses to 5-HT, decreased with length of storage of the ileum. If decreasing sensitivity to 5-HT (with time) is due to loss or dysfunction of 5-HT receptors on the ileum, the decrease in attenuation by lignocaine may also be mediated by this.

Discussion

Our findings are preliminary, but when considered alongside existing experimental and clinical data, may be interpreted as indicating an important role for alterations in 5-HT function in the perception of tinnitus.

Tinnitus is often preceded by auditory insults (such as noise or drug exposure) and these may evoke plastic changes in auditory areas of the CNS, including changes in 5-HT function at different levels in the CNS. Changes in 5-HT may be a com-

Table 2 Effects of lignocaine hydrochloride on the specific radioligand binding to the human serotonergic receptors and IC₅₀ values for the reference compounds

| Receptors | Lignocaine hydrochloride (% inhibition of control specific binding) | | Reference compounds | | |
|------------------------|--|-------|---------------------|-----------------------|-------|
| | 10 µM | 75 µM | Compound | IC ₅₀ (nM) | (nH) |
| 5-HT _{1A} | 10 | 16 | 8-OH-DPAT | 0.51 | (0.8) |
| 5-HT _{2A} | - | - | Ketanserin | 3.4 | (1.3) |
| 5-HT _{2C} | - | - | mesulergine | 2.6 | (1.3) |
| 5-HT ₆ | - | - | serotonin | 530 | (1.1) |
| 5-HT ₇ | - | - | serotonin | 1.9 | (1.0) |
| 5-HT _{uptake} | - | - | imipramine | 4.6 | (1.1) |

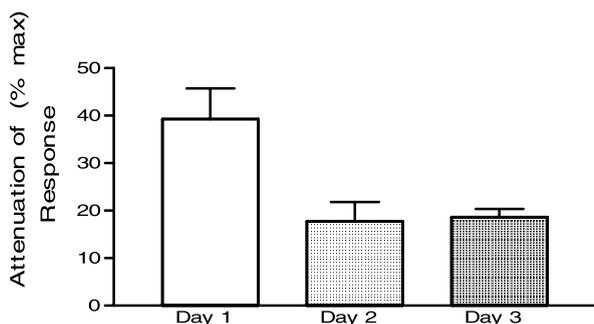
Mean values (n = 2) ≤ 10% inhibition 8-OH-DPAT (8-hydroxy-2-(di-n-propylamino) teraline)

Note: Of the receptors and functions tested, lignocaine hydrochloride showed significant inhibition (at potentially tinnitolytic concentration) at only 5-HT_{1A} receptors. If this inhibition were receptor mediated and competitive, a 7.5 fold increase in lignocaine concentration might be expected to produce inhibition of around 30% (at 75 µM) rather than the 16% indicated. However, it is possible that these concentrations of lignocaine do not fall on the linear part of the competition curve, or that the inhibition is non-competitive.

Table 3

| | Day 1 | | Day 2 | | Day 3 | |
|----------|-------|-------|-------|-------|-------|------|
| | Pre | Post | Pre | Post | Pre | Post |
| Mean | 68.1 | 23.7 | 68.7 | 51.3 | 77.8 | 57.4 |
| Variance | 496.6 | 397.8 | 488.2 | 183.7 | 195.5 | 24.0 |

Note: Values given are for % of maximal contraction pre (in absence of lignocaine) and post (in presence of 1.82×10^{-5} M Lignocaine), and are for approximately the same region on of the dose response curve (around 70% of maximal contraction). The large variances are a reflection of differences in response size (particularly due to the region of ileum used).



Graph 1

Note: This graph shows the attenuation in contraction (pre lignocaine minus post lignocaine) following 2 minutes pre-incubation with 1.82×10^{-5} M lignocaine (bath concentration) from Day 1 (immediately after removal of the ileum) to Day 3.

compensatory mechanism triggered by alterations in the activity of the other neurotransmitters [36], and indeed, 5-HT has been called “a stabilising agent which assists in returning the mind to its homeostatic set point” [37]. Dysfunction of such a compensatory mechanism, resulting in movement from a physiological “set point” could result in tinnitus. Alterations in the level of modulatory activity may be more important than the absolute levels of 5-HT. This may explain the paradoxical observation that lignocaine, in addition to having pronounced tinnitolytic properties, also has tinnitus as one of its most commonly occurring side effects [38].

There are numerous possible basis for such changes in 5-HT function, e.g. changes in receptor populations, to release or to uptake of 5-HT, and a number have been mentioned in the introduction. Other potential sites include 5-HT_{1B/D} receptors and agonists, the activity of which has been well characterised because of their use in the treatment of migraine. Binding by 5-HT (or 1_{B/D} agonists) to 1_{B/D} receptors, strongly inhibits release of (and hence transmission by) 5-HT. Activation of 1_B receptors also modulates 5-HT's interaction with other neurotransmitters, as previously discussed [4]. Both are important auto inhibitory mechanisms. Therefore dysfunction of 5-HT_{1B/D} receptors could result in changes to 5-HT's modulatory activity. 5-HT_{1A} and ₂ receptors have a similar distribution throughout the auditory centres [1,2]. If, as the binding

data indicate, 5-HT_{1A} receptors are influenced by lignocaine, there are many pieces of evidence which could be interpreted as supporting abnormal function of this receptor subtype in people with tinnitus [17,18,19].

Development of potential treatments

Many 5-HT active agents are already used clinically (e.g. selective serotonin re-uptake inhibitors in treatment of depressive disorders and 5-HT_{1B/D} agonists in migraine). Both 5HT₂ and 5-HT_{1B/D} agonists have already been shown to influence auditory processing [30,39]. There may be potential for development of these in the treatment of tinnitus perhaps using a combination of drugs with different properties, which are active at different sites. The fact that intranasally delivered lignocaine is effective in both migraine [40] and tinnitus (reported historically) may indicate a common target for prospective pharmaceutical treatments and hence, potential for some anti-migraine drugs. It is also possible that the lignocaine must reach the site at which it is active in a bolus for any tinnitolytic effect to become apparent. This may not occur when it is given by routes other than i.v.

It may be that lignocaine's tinnitolytic effects are less directly involved with 5-HT and that a slightly more abstract mechanism is responsible. For example, a selective effect at a sodium channel subtype, one which is unaffected by the other local anaesthetics. The effect of lignocaine in patients suffering from tinnitus may be enhanced by increased numbers of this particular subtype of channel. Expression of these channels could conceivably be increased by the pathological processes and plastic changes which result in tinnitus. For example, tinnitus is widely hypothesised to involve a degree of central re-organisation. This reorganisation is most likely the product of changes in synaptic function and formation of new contacts through “sprouting” of axonal processes. These reorganised areas containing the newly formed processes may have higher density of a particular subtype of sodium channels. This effect could occur in addition to or as the result of an interaction with 5-HT.

Better characterisation of lignocaine's activity is still required. Further work involving release studies, additional use of human 5-HT receptor

subtypes (e.g. $1_{B/D}$, $2B$, 6 and 7 as they become available) and clinical studies using measurement of evoked auditory responses (perhaps in conjunction with 5-HT active agents) are required. These may yield more specific information on the mechanism of an interaction with 5-HT function, allowing development of a rational for lignocaine tinnitolytic effects and a potential pharmaceutical treatment.

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Ginkgo biloba in the treatment of tinnitus: Preliminary results of a match-paired, double-blinded placebo-controlled trial involving 1115 subjects

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Previous studies concerning the possible therapeutic effect of Ginkgo biloba leaf extracts in the treatment of tinnitus are contradictory. The inconsistency of the results from such trials may have multiple explanations. Several of the published trials involved too few subjects to provide conclusive data whilst other trials have had inadequate controls and subject selection. This trial was undertaken in an attempt to provide a definitive answer as to the effectiveness of this material. In this match-paired, double-blinded placebo-controlled trial, the effect of 12 weeks treatment with Ginkgo biloba extract LI1370 on tinnitus was determined in 1115 healthy human subjects. Volunteers for the trial were obtained by national advertising and were drawn from all over the UK and Ireland. Extensive questionnaires covering many aspects of the nature of the tinnitus, the hearing status and the general well being were completed by all volunteers. Subjects selected for the trial were between the ages of 18 and 70, healthy and had experienced tinnitus for a minimum of 12 months. Assessment of tinnitus during the trial was made subjectively using shorter questionnaires covering the loudness, awareness and annoyance of the tinnitus. Subjects were required to take a tablet (containing 50 mg standardised extract or matching placebo) 3 times a day for 12 weeks and to complete 4 short questionnaires at various stages of the trial. Questionnaires 1, 2 and 3 were completed before commencement, at 4 weeks and 12 weeks into the trial respectively. Questionnaire 4 was submitted 2 weeks after completion of the treatment. Approximately 180 subjects began the trial in August/September 1998 and approximately 935 participants began the trial in January/February/March 1999. The final subjects are scheduled to complete the trial by the end of June 1999.

Introduction

There are at present no effective pharmacological treatments for Tinnitus. Since there is considered to be a number of underlying pathologies responsible for tinnitus it is unsurprising that there is not one single treatment for all sufferers. The absence of analysis based on tinnitus characteristics (such as underlying conditions and duration of tinnitus) may partly explain the inconsistent and modest positive results when testing possible therapeutic agents on small groups of tinnitus sufferers with many different underlying pathologies. The current study was carried out using a large number of tinnitus

patients, and some attempt was made to classify tinnitus characteristics. The therapy under test was LI1370, a standardised extract from the green leaves of Ginkgo biloba. LI1370 is standardised in the amount of ginkgo-flavone glycosides (24%) and terpenoids (6%) it contains, which are believed to be the active ingredients of the extract.

There have been more than 40 controlled trials; including several large well designed trials, to determine the effects of Ginkgo biloba on the symptoms of cerebral insufficiency [1,2]. Data from these trials have indicated that Ginkgo biloba can provide significant therapeutic effects on memory disturbances and other cognitive deficits, including tinnitus. In addition, there have been several studies carried out to determine whether Ginkgo biloba is successful in the treatment of tinnitus alone (with-

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out accompanying other symptoms of cerebral insufficiency). Unfortunately, many of these studies were small and not suitably controlled. A recent systematic review of the literature concerning the efficacy of Ginkgo biloba as treatment for tinnitus [3] discussed the results of five studies which were deemed to have had suitable controls, used patients whose primary complaint was tinnitus, and used undiluted Ginkgo biloba mono-therapy for treatment. Four out of five trials had positive outcomes. Ernst and Stevinson [3] concluded that the evidence to date is favourable to Ginkgo biloba as a treatment for tinnitus, but more large methodologically rigorous trials are needed to draw firm conclusions. The results presented here are preliminary data from a double-blind, randomised, trial on 1115 patients in which all stages of data acquisition and analysis have been very rigorous, endpoints are consistent, and classification of patients very thorough. Some data has yet to be collated and analysed at this time, therefore results presented in this paper are preliminary and are NOT yet complete. In order to maintain the double-blinded nature of the trial, some results (that had been compiled as of 31 July 1999) were unblinded by one of the independent code holders and are presented here.

Methods

Subjects

Trial participants were recruited by advertisements in the national press. All applicants were invited to complete a large computer readable questionnaire which included general background and health questions, along with detailed questions regarding tinnitus. 1115 healthy human subjects aged between 18 and 70 were selected and matched paired according to several criteria (Tables 1 and 2). All participants were fully informed as to the nature of the trial, their right to withdraw at any time, and the chances of the material being successful. All participants completed a signed consent form.

Table 1 Exclusion criteria

| |
|--|
| <ul style="list-style-type: none"> • Subjects under 18 or over 70 years of age • Pregnant females or females liable to become pregnant during the trial • Subjects previously taken Ginkgo biloba • Subjects who had had tinnitus less than 12 months • Subjects who deemed their tinnitus to have varied greatly in the 6 months preceding completion of the questionnaire (as opposed to not at all, slightly or moderately) • Subjects who had tried any of the defined therapies (TRT, acupuncture, homeopathy, hypnotherapy, relaxation therapy, drugs, herbs or any other therapy described apart from hearing aids) for their tinnitus in the 6 months preceding completion of the questionnaire • Subjects not in general good health • Subjects taking anticoagulation therapy • Subjects taking antidepressants • Subjects with abnormal blood pressure. |
|--|

Table 2 Matchpairing criteria

| | |
|---|--|
| • Gender | |
| • Age | |
| • Tinnitus Duration | |
| • Tinnitus Characteristics: (Hearing status/Likely cause of deafness/tinnitus) | |
| Group 1 | Presbycusis – hearing loss and tinnitus began after the age of 50 |
| Group 2 | Conductive Deafness – Have Otosclerosis |
| Group 3 | Vascular Origin – tinnitus changes with heart rate/pulse |
| Group 4 | Deaf – moderate /severe/ profound deafness (can hear well using hearing aid/difficulty hearing with a hearing aid/hearing aid of little benefit) |
| Group 5 | Perfect hearing/ slightly deaf (normal hearing/ difficulty hearing beyond 3–4 feet) |
| Group 5a | Noise induced – participants that believe their tinnitus may have been caused by noise exposure |
| Group 5b | Other – participants that do not believe that their tinnitus may have been caused by noise exposure |

Randomisation and match-pairing

Two named, independent people, held a randomised code for placebo and active tablets. The code was arranged into pairs by one of the code holders in order to enable match-pairing. Each pair of numbers encoded for one placebo and one active preparation. Selected and match-paired participants were assigned randomly to one set of paired codes from which each participant was allocated one of the preparations. The code was broken only in the case of possible severe adverse reaction, and could be broken without jeopardising the rest of the code

Trial design

Trial participants were instructed to take 3 tablets a day for 12 weeks and to complete 4 questionnaires. The first questionnaire (questionnaire 1) was completed before starting the tablets, a second questionnaire (questionnaire 2) was completed 4 weeks into the treatment, a third questionnaire (questionnaire 3) was completed upon finishing the tablets, and a fourth questionnaire (questionnaire 4) was completed 2 weeks after stopping the treatment (see Table 3).

Table 3 Time at which each Questionnaire was completed

| | | |
|------------------------|----------|---|
| Questionnaire 1 | 0 weeks | Before starting the tablets |
| Questionnaire 2 | 4 weeks | 4 weeks into the treatment |
| Questionnaire 3 | 12 weeks | At the end of the 12 weeks of treatment |
| Questionnaire 4 | 14 weeks | 2 weeks after completing the treatment |

Changes in tinnitus were assessed in two ways. Firstly, participants were directly asked whether their tinnitus had changed in either loudness or in how troublesome it was since starting the treatment (questionnaires 2 and 3) or since stopping the

treatment (questionnaire 4). Subjects were asked to score any changes in their tinnitus on a five-point scale with no change in the middle (see Table 4).

Table 4 Questions 8 and 10: Questions asked to determine the subjective effect of treatment

| | | |
|--------------------|---|-----|
| Question 8 | Do you think that the treatment you have taken as part of the trial has made your tinnitus: | |
| | Much louder? | [] |
| | Slightly louder | [] |
| | Unchanged | [] |
| | Slightly quieter | [] |
| | Much quieter | [] |
| | Disappear | [] |
| Question 10 | Do you think *the treatment has made your tinnitus: | |
| | Much more troublesome | [] |
| | Slightly more troublesome | [] |
| | Unchanged | [] |
| | Slightly less troublesome | [] |
| | Much less troublesome | [] |

*The word "stopping" is included here in questionnaire 4.

Secondly, participants were asked to assess the loudness, the variability, and the annoyance of their tinnitus under various conditions (e.g. loud/quiet environment and active/inactive) on a 5-point scale. The subjects were also asked to assess their awareness of their tinnitus throughout the day on a 10-point percentage scale. The answers to these questions in questionnaires 2, 3 and 4 will be compared to the answers to questionnaire 1 to determine whether there was any change in the patient's subjective assessment of their tinnitus.

In addition, participants were asked questions regarding compliance, other cerebral insufficiency symptoms, and side effects.

Preliminary data from the answers to the questions that directly asked the participants to assess any subjective changes in their tinnitus (8 and 10) are presented here. Data is presented from the answers to questions 8 and 10 in all questionnaires returned by 31 July 1999. All other data has not yet been analysed and will not be presented here. Full analysis of the data from this trial will be published at a later date.

Results

1115 participants started the trial, a summary of the characteristics of whom can be seen in Table 5. At the time of analysis (31 July 1999) 1067, 998, 902, and 901 questionnaires 1, 2, 3 and 4 had been returned respectively, 44 participants are known to have withdrawn, and the remainder are at present being chased up, as they have not returned all questionnaires. At this stage no data has been excluded due to withdrawals, or poor compliance. Exclusion of participants will be carried out if deemed necessary upon full analysis and will be carried out blinded.

A summary of the preliminary results from the answers to questions 8 and 10 in questionnaires 2, 3

Table 5 A summary of the characteristics of the 1115 participants who started the trial

| | |
|----------------------------------|--|
| Gender: | 770 Male, 345 Female |
| Age: | 19–69 mean 62, median 62 (standard deviation 4.6) |
| Tinnitus duration: | 1–69 years mean 12, median 9 (standard deviation 9.5) |
| Tinnitus Characteristics: | (see Table 2 for explanations) |
| | • 180 group 1 – Presbycusis |
| | • 14 group 2 – Conductive Deafness |
| | • 49 group 3 – Vascular Origin |
| | • 131 group 4 – Deaf |
| | • 196 group 5a – Perfect hearing/slight deaf (noise induced) |
| | • 545 group 5b – Perfect hearing/slight deaf (other) |

and 4 can be seen in Table 6. Throughout the trial (across questionnaires 2–4), 73–83% of the participants felt that their tinnitus had not changed in loudness, or in how troublesome it was. 6–10% of the participants felt that their tinnitus became quieter or less troublesome during the 12 weeks of treatment, and 13–15% felt that their tinnitus became louder or more troublesome upon stopping the treatment. However, 16–18% felt that their tinnitus became louder or more troublesome whilst on the treatment, and 4–9% felt that stopping the treatment made their tinnitus quieter or less troublesome.

Table 6 Summary data of the responses to questions 8 and 10 in questionnaires 2, 3 and 4: Numbers indicate the percentage of participants who responded to each of the answer options.

| Question 8 | Louder | No change | Quieter |
|----------------------------|------------------|-----------|------------------|
| Questionnaire 2 (4 weeks) | 18% | 76% | 6% |
| Questionnaire 3 (12 weeks) | 17% | 73% | 10% |
| Questionnaire 4 (14 weeks) | 15% | 79% | 6% |
| Question 10 | More troublesome | No change | Less troublesome |
| Questionnaire 2 (4 weeks) | 18% | 75% | 6% |
| Questionnaire 3 (4 weeks) | 16% | 74% | 9% |
| Questionnaire 4 (4 weeks) | 13% | 83% | 4% |

The unblinded results from the preliminary data can be seen in Table 7 and Figure 1. It is clear from the results that although some participants felt that their tinnitus had changed during the trial, there were no significant differences between the responses of participants receiving placebo and those receiving the active preparation.

Discussion

Despite the preliminary nature of the results presented here, the data strongly suggest that 3 × 50 mg/day Ginkgo biloba extract LI1370 for 12 weeks, has no greater therapeutic effect than placebo in the

Table 7 Responses to questions 8 and 10 in questionnaires 2, 3 and 4 (Q2, Q3, and Q4): The numbers correspond to the total number of active or placebo treated participants responding to each of the answer options

| Question 8 | No answer | | Much Louder | | Slightly Louder | | No change | | Slightly quieter | | Much Quieter | | Disappear | |
|-------------------|-----------|---|-------------|----|-----------------|----|-----------|-----|------------------|----|--------------|---|-----------|---|
| | A | P | A | P | A | P | A | P | A | P | A | P | A | P |
| Active or Placebo | | | | | | | | | | | | | | |
| Q.2 (4 weeks) | 1 | 1 | 14 | 13 | 76 | 76 | 377 | 379 | 28 | 30 | 0 | 2 | 0 | 1 |
| Q.3 (12 weeks) | 1 | 0 | 13 | 10 | 66 | 65 | 325 | 335 | 40 | 34 | 6 | 7 | 0 | 0 |
| Q.4 (14 weeks) | 1 | 0 | 10 | 12 | 55 | 55 | 361 | 355 | 19 | 29 | 2 | 2 | 0 | 0 |

| Question 10 | No answer | | Much more troublesome | | Slightly more troublesome | | No change | | Slightly less troublesome | | Much less troublesome | |
|-------------------|-----------|---|-----------------------|---|---------------------------|----|-----------|-----|---------------------------|----|-----------------------|---|
| | A | P | A | P | A | P | A | P | A | P | A | P |
| Active or Placebo | | | | | | | | | | | | |
| Q.2 (4 weeks) | 3 | 3 | 13 | 5 | 76 | 89 | 379 | 374 | 23 | 32 | 0 | 1 |
| Q.3 (12 weeks) | 2 | 1 | 14 | 8 | 60 | 65 | 333 | 337 | 39 | 33 | 5 | 5 |
| Q.4 (14 weeks) | 3 | 1 | 8 | 6 | 51 | 51 | 370 | 374 | 14 | 18 | 2 | 3 |

treatment of tinnitus. It is conceivable that upon complete analysis (including analysis of subgroups based on tinnitus characteristics), there may be a small group of tinnitus participants that are more responsive to the active preparation than the placebo, however at this stage this seems unlikely.

The results from the current trial are in accordance with some previous reports and in contrast to

other reports. Since this is the largest trial to date and was carefully designed and well controlled, it seems likely that the inconsistency of previous results is due to both the small number of participants involved, and the lack of placebo controls. However, since a recent trial [4] demonstrated that Ginkgo biloba significantly improved short term memory when administered in large (120 mg) sin-

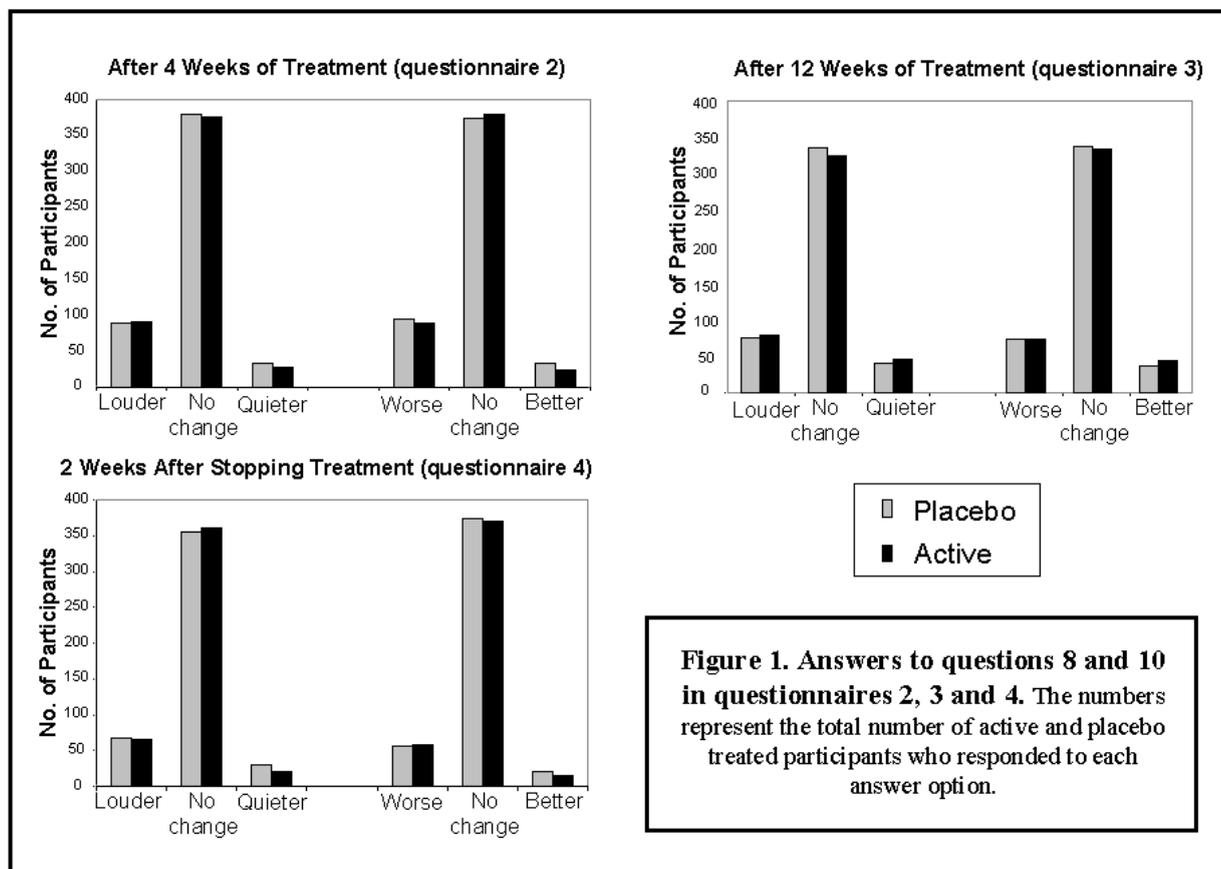


Figure 1 Answers to questions 8 and 10 in questionnaires 2, 3 and 4

gle daily doses, but was ineffective when administered in multiple small doses (3×50 mg/day), at least some of the inconsistencies may be related to the different dosing regimes.

An important observation from this trial is the large proportion of participants who found that their tinnitus became worse whilst being on the trial. The worsening response is most unlikely an effect of Ginkgo biloba, but is rather the effect of the attention to the tinnitus that is elicited by the questionnaires and tablets, as it existed equally in the placebo group. This is an unfortunate and unavoidable side effect of any trial involving tinnitus, and should be taken into consideration when designing future trials (i.e. minimise the frequency of both the therapy and tinnitus assessment).

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Gender aspects related to tinnitus complaints

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Speaking with patients whose tinnitus gives rise to emotional distress it is essential to focus on relevant gender-related factors. Males, in general, tend to ignore psychological ill health more than females. It has been shown by Dineen et al. [1] that the profile of tinnitus-related distress is somewhat different in the male patients whose stress seems to be more related to personality than emotions, as is the case for the female sufferers. The Nottingham Health Profile (NHP), designed for the measurement of health-related quality of life in medical conditions, was used in a tinnitus population including 57 females and 129 males [2]. The severity rate for four out of six dimensions of the NHP was higher among the females. Younger women reported significantly more health problems compared to a normal female control group in four dimensions; lack of energy, pain, emotional reactions and sleep disturbances.

Introduction

Gender as an explanatory factor in research of disease, etiology and illness behavior has in the past largely been ignored. There are examples in the literature of studies investigating the psychological profiles of tinnitus patients including men only. Using the male as the norm without considering aspects of gender limits the conclusions that can be drawn. To have a gender perspective when conducting a clinical interview is one way of identifying gender-related factors for descriptive and rehabilitative purposes as well as of obtaining relevant and interesting questions for research. Men tend to ignore their psychological ill-health more than women in our society, and men are more unlikely to report distress on psychometric scales. However it has been observed that the frequency of personality disturbances is higher in males than in females [3]. Dineen and his colleagues [1] showed that female subjects, in comparison with male subjects, reported a higher level of emotional reaction to their tinnitus. The distress of the male patients was more related to personality than emotion related, as was the case for the women. These latter findings support the general gender difference in the profiles of psychological health found by Horwitz and White [3]. The Nottingham Health Profile (NHP), used in

this study, has been proven to be a reliable and valid instrument for the assessment of health-related quality of life in various medical conditions.

Aims in the present study were: *to examine the relationship between level of hearing and specific tinnitus-related distress and to make gender-based comparisons of general health-related quality of life between the studied group and a normative Swedish population sample.*

Method

Subjects

The subjects (N = 186) participating in the study were 57 females (30.4%) and 129 males (69.6%), a group of consecutive tinnitus patients consulting an audiological clinic during a period of six months.

Instruments

General health-related quality of life was assessed with the Swedish version of the NHP [4]. The first part (NHP I) comprises six different dimensions: lack of energy, pain, emotional reactions, sleep, social isolation and mobility problems; all together 38 yes/no questions. The second part (NHP II) includes seven yes/no statements of health-related problems in daily life. Specific tinnitus-related distress was assessed with the Tinnitus Severity Questionnaire (TSQ) with ten items, each yielding scores from 0 = not affected to 4 = always affected. The maximum score is 40.

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Procedure

The target group comprised 186 consecutive tinnitus patients who were asked by letter to fill in two self-assessment scales (TSQ and NHP) mailed to their home address prior to the first tinnitus consultation. They were asked to bring the filled in questionnaire to the group information meeting. Standard audiometric assessments were carried out. Of those who had been contacted 98% returned the filled in questionnaire.

Results and discussion

Level of hearing (Standard audiometric assessments) did not seem to play a significant role for the experience of specific tinnitus-related distress (TSQ), but the more severe the hearing loss the more negative the impact on the day to day living (NHP II), i.e. work, social relationships, family life, sex life, and leisure time etc. The mean age of the female and the male subjects was approximately 55 (SD: 18.2; age range: 86–21) and 49 (SD: 15.1; age range: 86–15) years respectively, a statistically significant difference ($p < 0.05$).

Patterns of health in the present study seem to be gender-related. In general, women had more severe health problems than men. A gender difference was observed for four of the six dimensions of the NHP I; "Pain" ($p < 0.01$), "Mobility" ($p < 0.01$), "Sleep" ($p < 0.05$) and "Lack of energy" ($p < 0.05$). Younger and middle-aged female patients exhibited most signs of neagative health status as compared to their matched age-category. The results for the NHP II showed that "Occupational life" (Question 39) was perceived as significantly more problematic by the men than by the women ($p < 0.001$). In contrast, the female patients reported that "Domestic work" (Q 40) and "Holidays" (Q 45) were areas of life that they perceived as most distressing ($p < 0.001$; $p < 0.0001$). No statistically significant gender differences were, however, found in the four domains: "Sex life" (Q 41), "Social life" (Q 42), "Hobbies" (Q 43), and "Relationships" (Q 44).

Throughout, the comparisons made with normal control samples in each age-category showed that the scores for males with tinnitus were higher for two dimensions, "Sleep" and "Emotion". Men in age-group 55–64, demonstrated a significantly raised level of emotional reactions and sleep problems. The opposite was true for women in the same age-group; they did not report significantly more health problems compared to normal controls. One important dimension of quality of life is sleep. Sleep

disturbances seem to play a crucial role in the pathogenesis of psychiatric illnesses and have been identified in a number of psychiatric disorders: Schizophrenia, mood disorders, anxiety disorders, panic disorders, alcoholism, and dementia [5]. In the present study, sleep disturbances seemed to be the most commonly experienced difficulty when compared with normal control groups.

Conclusion

Health profiles, measured with a generic instrument like the NHP contribute to the explanation of tinnitus severity, especially as an indicator of mood states and how this influences quality of life. A gender difference in the perceived quality of the tinnitus sound has previously been observed [6,1], i.e. women more often than men report a greater variety of sounds. We are interested in further investigating how the complexity of sounds is linked to emotional aspects, etiology, and quality of life as complex tinnitus sounds also seem to correlate with tinnitus distress.

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Early identification of therapy resistant tinnitus

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Introduction

The majority of patients seeking help and treatment for tinnitus, experience a lessening of their symptoms after a time period of 18 months after their first tinnitus consultation. The exception to this rule is the “therapy resistant” patient, whose sometimes very troublesome symptoms show no sign of diminishing with time. In a previous study, the authors used the Nottingham Health Profile (NHP) in order to investigate factors that would help predict the severity of tinnitus symptoms as measured by the instrument “Tinnitus severity Questionnaire” (TSQ). The sub-scales of the NHP, which were found to predict tinnitus suffering were; “emotional reactions”, “pain” and “sleep disturbances” [1]. The hearing thresholds did not emerge as predictors. The severity of tinnitus has recently been reviewed and the most commonly reported findings were the strong impact on the severity of tinnitus by psychological factors. The correlation between hearing parameters and tinnitus severity [2] was weak. It has also been reported that occurrence of depressive and anxiety-related symptoms in tinnitus patients are remarkably high [3,4] and that depressive and anxiety disorders had debuted before the onset of tinnitus which indicate that tinnitus is secondary to these symptoms [4].

The AIM of the present study was to investigate risk factors for “therapy resistant” tinnitus as measured by absence from work, related to tinnitus (AWT).

Method

The study included 172 consecutive tinnitus-patients consulting an audiological physician at the Department of Audiology at Sahlgrenska University Hospital during a 6 months period (54

women and 118 men). The mean age of the women (57 ± 16 years) were significantly higher than the men (52 ± 13 years), ($p = 0.006$), but no statistical difference were found in pure tone averages between gender nor between the experimental group and drop-outs (see Table 1).

Table 1 The hearing thresholds are presented in relation to gender.

| | PTA 0.5; 1; 2 kHz | PTA 3; 4; 6 kHz |
|-----------|-------------------|-----------------|
| Women | 20 ± 16 dB HL | 32 ± 22 dB HL |
| Men | 15 ± 15 dB HL | 40 ± 24 dB HL |
| Drop-outs | 15 ± 14 dB HL | 37 ± 20 dB HL |

The patients were re-assessed 18 months later in order to identify and investigate the “therapy resistant” patients. The working definition of “therapy resistant” that was used, was the patient’s absence from work related to tinnitus (AWT). There were 127 patients (74%) who fulfilled the follow-up and there were 45 dropouts (26%).

Another 38 patients had been retired due to age and 10 patients had been retired due to sickness prior to the investigation.

Analyses of interviews and questionnaire data were conducted, and information was collected regarding the patients’ sick-leave statistics after their first tinnitus consultation. The relations between the risk factors and AWT were statistically analysed using Fisher’s permutation test. The significant factors were included in a logistic regression model, resulting in a risk score.

Results

In the study 18 out of the 79 patients were absent from work due to tinnitus (AWT+). These 18 patients had varying diagnoses and these are presented in Table 2. The AWT-variable was significantly correlated to the Body Mass Index, and to the NHP subscales: “Emotional disturbances”, “Sleep disturbances”, “Energy”, “Pain”, “Physical mobility” and “Social isolation”. There were also significant correlations between the TSQ including

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questions concerning how much tinnitus reduces the overall quality of life, how often tinnitus is noticed during the waking hours or impairs concentration, and how often tinnitus makes the patients feel anxious or worried, tense or irritable or depressed and miserable.

Table 2 The specific diagnoses of the AWT group.

| Diagnosis | Patients |
|-----------------------------------|----------|
| Tinnitus | 3 |
| Heart problems and tinnitus | 2 |
| Atralgia and tinnitus | 2 |
| Backpain and tinnitus | 2 |
| Depression and tinnitus | 2 |
| Hearing loss and tinnitus | 2 |
| Vertigo, depression and tinnitus | 1 |
| Headache, anxiety and tinnitus | 1 |
| Anxiety and tinnitus | 1 |
| Whiplash and tinnitus | 1 |
| Atralgia, depression and tinnitus | 1 |

Age, gender, high frequency hearing loss, degree of education, income level, alcohol consumption and smoking were not related to AWT.

The main predictors influencing AWT as estimated by the logistic regression analyses were the NHP questions concerning depression and reduced mobility, but also physical exercise on a regular basis and hearing thresholds over both ears for the low and mid frequencies. Interestingly, the AWT+ patients with reduced mobility had high scores on the psychological part of the TSQ. The probability of AWT in relation to the predictors is shown in

Figure 1. Consequently, the higher the risk point value, the higher the probability for the individual to be absent from work. The calculated probability for AWT+ by this model was 26%, but the true observations were 23% (i.e. 18 patients out of 79). For approximately 15% of the patients the probability was very high and for 35% of the patients the estimated probability was very low.

Drop-outs: The profile of the drop-outs could also be assessed at the first visit to the clinic, and was compared to the profile for the examined group at the same occasion. There were no differences between the dropouts and the examined group in NPH- subscales, the 10 items of the TSQ and the hearing thresholds of the low or mid frequencies.

Discussion

Based on our present results we are now introducing the following definitions. The definitions represent 3 categories, distinguished from each other concerning the causes of tinnitus. The categories are as follows:

- Central tinnitus;
- Auditory tinnitus;
- Somatic tinnitus.

The etiology of tinnitus is defined as central if the causality is related to psychiatric disorders, as auditory if the causality relates to damage of the inner ear or other parts of the auditory pathways and as

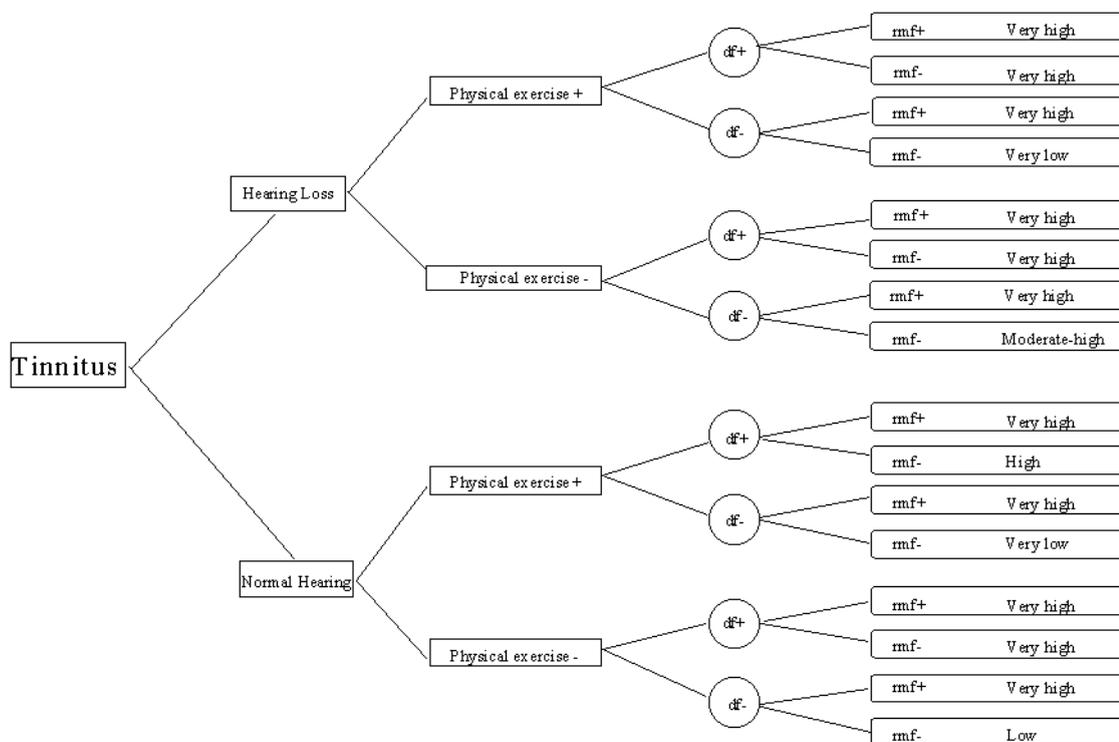


Figure 1: The probability of AWT is presented in relation to the depression factor (df), reduced mobility factor (rmf), physical exercise and hearing.

somatic if the causality relates to somatic illness or poor health [2]. Patients with central tinnitus are offered psychiatric/psychological treatment, while patients with auditory tinnitus are referred to audiological rehabilitation and patients with somatic tinnitus are treated according to their somatic disorders. A combination of these rehabilitation strategies could also be given since patients can have a combination of these 3 etiologies.

The key factors for defining "therapy resistance" were in our present study: anxiety, depression, limited mobility, hearing impairment, and physical exercise on a regular basis. Psychological factors were the most important predictors for therapy-resistant tinnitus, which is in accordance with other investigations [4–10]. In the present study the patients, which were regarded as suffering from somatic tinnitus, also scored high on the psychological part of the TSQ indicating a covariation between limited mobility and depression.

The comorbidity between somatic symptoms and depression is well known and it was demonstrated in a multicenter study including 15 primary health clinics that patients with depressive disorders complained primarily of somatic symptoms (41%), pains (37%), and fatigue and sleep problems (12%) [11].

In our opinion it is of great importance to identify and treat depression and anxiety disorders initially, so the risks for the process developing from emergency of tinnitus to tinnitus becoming persistent and severe will be minimised. By using a screening procedure at the first visit to the clinic these factors could be identified and we suggest the use of the Nottingham Health Profile as a complement to tinnitus specific questionnaires. One approach to improve the benefit of different treatments could be to focus on causality as a factor for the severity of tinnitus.

The analysis in the present study showed that the model predicted therapy resistance very accurately. This allows identification of high-risk patients. It also facilitates the identification of low risk patients who might not be in need of extensive efforts from the medical establishment. The results of the present study can also be used, as a basis for decisions regarding the level or the amount of medical and rehabilitation measures needed for a given patient.

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Effects of insomnia on tinnitus severity: A follow-up study

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Purpose: To investigate the effects of insomnia on tinnitus severity and to determine how this relationship may evolve with the passage of time.

Methods: Questionnaires were mailed to patients prior to their initial appointment at the Oregon Health Sciences University Tinnitus Clinic between 1994–1997. These questionnaires requested information pertaining to insomnia, tinnitus severity and loudness. During their initial appointment, patients received counseling, education and reassurance about tinnitus; audiometric and tinnitus evaluations; and treatment recommendations. Follow-up questionnaires were mailed to 350 patients one to four years (mean = 2.3 years) after their initial appointment at the Clinic.

Results: One hundred seventy four patients (130 males, 44 females; mean age 55.9 years) returned follow-up questionnaires. Even though many of these patients improved in both sleep interference and tinnitus severity, a significant number (43) reported on the follow-up questionnaire that they continued to have difficulty sleeping. Reported loudness and severity of tinnitus were significantly greater for this group than for groups of patients who reported that they never or only sometimes have difficulty sleeping. The relationship between sleep disturbance and tinnitus severity became more pronounced with the passage of time.

Conclusions: Insomnia is associated with greater perceived loudness and severity of tinnitus. These findings underscore the importance of identification and successful treatment of insomnia for patients with tinnitus.

INTRODUCTION

Tyler and Baker [1] asked patients to list the difficulties they experienced as a result of their tinnitus. The most frequently listed difficulty was “getting to sleep,” reported by 41 (56.9%) of the 72 respondents. Jakes *et al.* [2] and Axelsson and Ringdahl [3] also reported that insomnia was the problem most frequently mentioned by tinnitus patients.

Sanchez & Stephens [4] mailed Tyler and Baker’s questionnaire to 436 patients who were scheduled to visit the Tinnitus Clinic of the Welsh Hearing Institute. Sleep difficulty was the second most common complaint, listed by 25% of the respondents. Hearing problems, the most common difficulty, was mentioned by 30% of the patients. Hallam *et al.* [5] reported that the three main areas of complaint identified by 79 tinnitus patients at a neuro-otology clinic were emotional distress,

hearing difficulties, and sleep disturbance. Hallam [6] estimated that approximately 50% of tinnitus patients experience disturbances of the normal sleep pattern.

In their study of tinnitus severity, Meikle *et al.* [7] analyzed responses to questionnaires from more than 1800 patients who attended the Tinnitus Clinic at Oregon Health Sciences University. There was no correlation between self-rated tinnitus severity and the loudness, type, quality, or pitch of tinnitus sounds heard by patients. However, tinnitus severity ratings were highly correlated with sleep disturbance. Axelsson and Ringdahl [3], Scott *et al.* [8], Erlandsson *et al.* [9], and Alster *et al.* [10] also reported that tinnitus was more severe in patients who experienced insomnia.

It is clear that sleep disturbance is a major problem for many people with tinnitus. The goal of the present study was to investigate the effects of insomnia on tinnitus severity and to examine how this relationship may evolve with the passage of time. Ultimately we hope that this information will (1) be used for developing and implementing effective treatment programs; and (2) contribute to the development and refinement of diagnostic and assessment procedures for tinnitus.

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Methods

Detailed questionnaires were mailed to patients prior to their initial appointment at the Oregon Health Sciences University Tinnitus Clinic between 1994–1997. These questionnaires requested information about patients’ medical, hearing, and tinnitus histories [11–12]. The initial appointment at the Clinic had the following format – many of these procedures were described by Johnson [12]:

(1) Patients met with staff members for an in-depth interview and review of their medical, hearing, tinnitus, and psychosocial histories and conditions. Patients received information about possible causes of their tinnitus as well as reassurance and counseling regarding factors that could exacerbate or improve their condition.

(2) Audiological evaluations which included pure tone air and bone conduction thresholds; speech perception in quiet and noise; MCL/UCL; and tympanometry.

(3) Tinnitus evaluations which included matching tinnitus to sounds played through headphones; determination of minimum masking levels; and measurements of residual inhibition.

(4) Evaluations of acoustic therapies: based on the patient’s audiological evaluations, various devices would be demonstrated. These could include hearing aids, ear maskers (a.k.a. sound generators), tinnitus instruments (combinations of hearing aids + maskers), tabletop sound generation machines, masking tapes or CDs.

(5) Review of the results of evaluations; presentation of treatment plan and other recommendations.

Follow-up questionnaires were mailed to 350 patients one to four years (mean = 2.30 ± 0.76 years) after their initial appointment. Appendix 1 contains a copy of the follow-up questionnaire. These questions were also asked in the initial questionnaires. Questions one through eleven constitute a Tinnitus Severity Index [13,14] (TSI) which assesses the negative impacts of tinnitus upon patients. Numerical responses to questions one through eleven were added together to give a total

TSI score for each patient. Data relating to patient demographics, audiometric thresholds, reported tinnitus loudness, and reported sleep disturbance were analyzed for patients who returned follow-up questionnaires.

Results

One hundred and seventy four patients (130 males, 44 females) returned follow-up questionnaires. This higher percentage of males is consistent with the usual percentage (>70%) of males seen in this Clinic. Table 1 contains grand averaged pure tone air conduction thresholds and standard deviations for all 174 patients. This pattern of high-frequency sensorineural hearing loss is typical for our patient population.

For the remaining analyses of initial and follow-up questionnaires, patients were divided into three groups based on their response to question 12: “Does your tinnitus interfere with sleep?” Table 2 contains the numbers of patients who answered “No,” “Yes, sometimes,” or “Yes, often” to this question. The net improvement in sleep disturbance from the initial to the follow-up questionnaire was as follows: eleven males and seven females moved from the “Often” group to the “No” group; one female moved from the “Often” group to the “Sometimes” group.

Comparisons of averaged audiometric thresholds among the “No,” “Sometimes,” and “Often” groups revealed no significant differences on either the initial or follow-up questionnaires. That is, there were no significant differences in hearing loss among groups of tinnitus patients with differing degrees of sleep disturbance.

Table 3 contains the mean ages and standard deviations of each group of patients (“No, Sometimes, Often”). The age range for patients making their initial visit to the Clinic was 17 to 83 years. The age range for patients who returned the follow-up questionnaire was 20 to 85 years. Comparing the average age of each group at the time of the patients’

Table 1 Grand averages of pure tone air conduction thresholds of patients (dB HL)

| (Hz) | 250 | 500 | 1000 | 2000 | 3000 | 4000 | 6000 | 8000 |
|-----------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Right ear | 14.3 ± 11.2 | 12.9 ± 12.0 | 16.5 ± 14.1 | 21.9 ± 19.7 | 33.1 ± 24.1 | 43.3 ± 25.6 | 46.2 ± 25.0 | 47.9 ± 27.4 |
| Left ear | 15.5 ± 14.4 | 14.3 ± 15.4 | 16.5 ± 16.8 | 24.6 ± 21.5 | 36.7 ± 23.9 | 44.8 ± 25.4 | 47.6 ± 24.8 | 50.1 ± 26.5 |

Table 2 Patients’ responses to “Does your tinnitus interfere with sleep?”

| | Initial | | Follow-up | |
|-----------|---------|---------|-----------|---------|
| | Males | Females | Males | Females |
| No | 34 | 8 | 45 | 15 |
| Sometimes | 52 | 18 | 52 | 19 |
| Often | 44 | 18 | 33 | 10 |
| Total | 130 | 44 | 130 | 44 |

Table 3 Average ages of patients (years)

| | Initial | Follow-up |
|---------------|-------------------------|-------------------------|
| No | 57.1 ± 11.2 (n = 42) | 57.7 ± 10.2 (n = 60) |
| Sometimes | 54.0 ± 11.0 (n = 70) | 55.9 ± 12.9 (n = 71) |
| Often | 50.7 ± 12.0 (n=62) | 53.6 ± 10.8 (n = 43) |
| Grand average | 53.6 ± 11.6 | 55.9 ± 11.6 |

initial appointment, the only significant difference is greater age for those who reported no sleep disturbance than for those who reported that they often have trouble sleeping ($p = 0.022$). There were no significant differences in age among the three groups of patients responding to the follow-up questionnaire.

Table 4 contains distributions of patients according to the number of years since tinnitus onset at the time of their initial appointment. Greater sleep disturbance is correlated with a higher percentage of patients whose tinnitus began within two years of their initial appointment. For example, 33.3% of the patients with no sleep interference had tinnitus that began within two years of their initial appointment. This percentage increases to 47.1% for patients who reported that they sometimes have difficulty sleeping, and it increases to 61.2% for patients who reported that they often experience insomnia. In general, patients with tinnitus that began within two years were more likely to experience sleep difficulties than patients who had tinnitus for three or more years.

Table 4 Years since onset of tinnitus at the time of initial appointment vs. numbers of patients reporting sleep difficulty

| Years | <1 | 1-2 | 3-5 | 6-10 | 11-20 | >20 |
|-----------|----|-----|-----|------|-------|-----|
| No | 9 | 5 | 1 | 6 | 12 | 9 |
| Sometimes | 19 | 14 | 12 | 6 | 6 | 13 |
| Often | 23 | 15 | 6 | 4 | 8 | 6 |

Table 5 contains means and standard deviations of reported loudness (on a 1-to-10 scale) of tinnitus for each of the three sleep interference groups on both the initial and follow-up questionnaires. Significant differences in reported loudness occurred between the group of patients who often have trouble sleeping and the groups who never or sometimes have sleep disturbance ($p \leq 0.0005$ for all of these comparisons on both questionnaires).

Table 5 also contains means and standard devi-

ations of TSI scores for each of the three sleep groups on both questionnaires. One-way analyses of variance indicated that there was a significant difference in TSI scores among the three sleep groups on both the initial ($F = 31.0$; $p \leq 0.0005$) and follow-up ($F = 59.5$; $p \leq 0.0005$) questionnaires. Results of multiple comparisons (Scheffe tests) of TSI scores made among the three sleep groups are listed in Table 5. In general, TSI scores increase significantly with reported sleep interference on both the initial and follow-up questionnaires.

The mean numerical response to almost every TSI question was significantly greater for the "Often" group compared to either the "No" or "Sometimes" sleep interference groups. The two exceptions were "Does your tinnitus make it harder to interact pleasantly with others?" and "Does your tinnitus interfere with your social activities or other things you do in your leisure time?" on the initial questionnaire.

There were significant differences in mean responses between the "No" and "Sometimes" groups for five of the TSI questions (those pertaining to discomfort in a quiet room, feeling irritable or nervous, feeling tired or stressed, difficulty relaxing, and usual discomfort experienced) on the initial questionnaire. However, significant differences in responses between these two groups of patients were seen for all eleven TSI questions on the follow-up questionnaire. Responses from the "Often" sleep interference group were significantly greater than those given by either of the other two groups for all eleven TSI questions on the follow-up questionnaire.

Discussion

Audiometric thresholds: Most of the patients in this study had bilateral high frequency sensorineural hearing loss beginning between 2000-3000 Hz. However, pure tone air conduction thresholds of patients with greater reported sleep interference

Table 5 Means and standard deviations of responses

| | Initial questionnaire | | | Follow-up questionnaire | | |
|---|-------------------------|--------------------------------|----------------------------|-------------------------|--------------------------------|----------------------------|
| | Group 1 No n = 42 | Group 2 Sometimes n = 70 | Group 3 Often n = 62 | Group 1 No n = 60 | Group 2 Sometimes n = 71 | Group 3 Often n = 43 |
| Reported loudness of tinnitus | 5.74 ± 1.89 | 6.23 ± 1.90 | 7.78 ± 1.75 | 5.53 ± 2.26 | 6.17 ± 1.89 | 7.92 ± 1.62 |
| TSI score | 28.46 ± 8.81 | 33.18 ± 6.60 | 40.09 ± 6.62 | 25.12 ± 7.79 | 31.58 ± 5.94 | 39.93 ± 6.56 |
| Scheffe comparisons of reported loudness between groups | 1 and 2 | 1 and 3 | 2 and 3 | 1 and 2 | 1 and 3 | 2 and 3 |
| p ≤ | 0.442 | 0.0005 | 0.0005 | 0.184 | 0.0005 | 0.0005 |
| Scheffe comparisons of mean TSI scores between groups | 1 and 2 | 1 and 3 | 2 and 3 | 1 and 2 | 1 and 3 | 2 and 3 |
| p ≤ | 0.006 | 0.0005 | 0.0005 | 0.0005 | 0.0005 | 0.0005 |

were not significantly different from thresholds of patients with fewer sleep disturbances. This observation is in contrast to the findings of Alster *et al.* [10] who reported that greater sleep disturbance was correlated with greater hearing loss in their study of 80 tinnitus patients. There are several possible explanations for the differing results of these studies: (1) patients in the study by Alster *et al.* were significantly younger (mean age 36 ± 11 years) than the patients in the present study (mean age 53.6 ± 11.6 years at the time of their initial appointment); (2) a greater percentage of Alster *et al.*'s patients were male (95.0% vs. 74.7% in the present study); (3) all of Alster *et al.*'s patients had been Israeli army personnel, 95% of whom had noise induced hearing loss – NIHL; (4) the average hearing loss for Alster *et al.*'s NIHL patients was 46 dB HL in the frequency range between 2–8 kHz; the average hearing loss across the same frequency range for patients in the present study was 39.6 dB HL. Any or all of these factors could have contributed to the association between sleep interference and audiometric data observed in each of these studies.

Time since onset of tinnitus: In the present study, tinnitus that had its onset within two years of the patients' initial appointment was correlated with a greater probability of sleep interference than tinnitus that had been present for three or more years (Table 4). Tyler and Baker [1] reported that the number of problems experienced by tinnitus patients decreased with increased time since the onset of their tinnitus. Similarly, Scott *et al.* [8] reported that their patients' tolerance to tinnitus increased with time since tinnitus onset. These observations could be part of the reason that patients with recent-onset tinnitus in the present study were more likely to experience sleep interference than patients who had tinnitus for three years or more. Increased tolerance to tinnitus over time probably also contributed to the net improvement of sleep patterns experienced by patients from the time of the initial to the follow-up questionnaires.

Loudness of tinnitus: Patients who often experienced sleep interference in the present study rated their tinnitus as significantly louder (on a 1-to-10 visual scale) than patients who never or sometimes experienced sleep disturbances. This association between sleep difficulty and reported tinnitus loudness was also observed by Slater and Terry [15]. Meikle *et al.* [7] reported that tinnitus severity was not correlated with the *matched* loudness of the sound. Tinnitus loudness reported on a visual scale might be a better indicator of perceived severity than tinnitus loudness that is matched to a sound presented through headphones.

Conclusions

(1) In the present study, greater sleep interference was correlated with greater tinnitus severity. This conclusion is in agreement with the findings of several other studies.[3,7–10]

(2) Differences in tinnitus severity among the three sleep interference groups were more pronounced on the follow-up questionnaire than on the initial questionnaire. A possible explanation for this is that the passage of time – an average of 2.3 years – from the initial to the follow-up questionnaire reduced the influence of earlier tinnitus onset observed on the initial questionnaire. By the time that they completed the follow-up questionnaire, all 174 patients in the present study had experienced tinnitus for more than one year, and the average time since the onset of their tinnitus had increased by 2.3 years.

(3) Comparing their responses on the initial and follow-up questionnaires, patients in the present study reported an overall improvement in both sleep interference and tinnitus severity. There are several factors which contributed to these improvements:

- (a) Patients received information about tinnitus; reassurance and counseling; audiometric and tinnitus evaluations; and treatment recommendations during their initial appointment.
- (b) Patients implemented recommended treatments including masking tapes or CDs; bedside sound generating machines; ear maskers, hearing aids, or combination instruments (combinations of hearing aids + maskers); relaxation and stress management therapies; psychological counseling; changes in diet (e.g. reducing intake of caffeine or alcohol); protecting their ears from excessively loud sounds; massage, exercise, biofeedback; and medications to improve sleep. Table 6 lists the medications that were taken for insomnia, depression, and anxiety by patients in the present study. In addition to any anxiolytic or antidepressant actions they might have, most of these medications can produce drowsiness and reduce sleep disturbances. In their study of the effectiveness of nortriptyline in tinnitus treatment, Dobie *et al.* [16] stated that "Insomnia is a prominent component of distress for tinnitus patients, with and without major depression, and adequate antidepressant therapy usually improves sleep." For some patients, over-the-counter sleep aids – including melatonin [17] – provide sufficient relief from insomnia.
- (c) The combination of information gathering, reassurance, and the implementation of effective treatment programs enables many tinnitus patients to improve their coping skills and to develop the ability to divert their attention away from their tinnitus. Patients often require substantial amounts of time after the onset of tinnitus to develop these types of adaptive strategies. Findings from the present study as well as those by Tyler and Baker [1] and Scott *et al.* [8] indicate that tinnitus severity tends to decrease with increased time from its onset.

Even though many patients in the present study improved in both sleep disturbance and tinnitus

Table 6 Medications used by patients in the present study

| | Number of patients using |
|---------------------------------|--------------------------|
| HYPNOTICS | |
| ZOLPIDEM (Ambien) | 2 |
| ANXIOLYTICS/SEDATIVES | |
| ALPRAZOLAM (Xanax) | 14 |
| CLONAZEPAM (Klonopin) | 3 |
| DIAZEPAM (Valium) | 1 |
| LORAZEPAM (Ativan) | 5 |
| ANTIDEPRESSANTS | |
| AMITRIPTYLINE (Elavil, Etrafon) | 10 |
| FLUOXETINE (Prozac) | 7 |
| NEFAZODONE (Serzone) | 2 |
| NORTRIPTYLINE (Pamelor) | 1 |
| PAROXETINE (Paxil) | 3 |
| SERTRALINE (Zoloft) | 1 |
| TRAZODONE (Desyrel) | 4 |
| VENLAFAXINE (Effexor) | 1 |

severity, there were still 43 patients who reported on the follow-up questionnaire that they “often” have

difficulty sleeping. These patients also reported that their tinnitus seemed louder and more severe than other patients in the study who had less sleep disturbance. In order to reduce the severity of tinnitus for these patients, it is imperative to treat their insomnia. The 43 patients in the “often” sleep disturbed group were contacted and advised about possible treatments for insomnia. In extreme cases, it might be advisable for a patient to visit a specialized sleep clinic.

Stouffer *et al.* [18] asked 528 patients to rate different conditions that reduced the severity of their tinnitus. The condition mentioned most often was sleep, by 26% of the respondents. The next two conditions mentioned most often were listening to TV or radio (by 23% of respondents) and being in a noisy environment (by 19%). The findings of this and the present study underscore the importance of identifying and treating insomnia when it is coincident with tinnitus. Improved sleep patterns can reduce the perceived severity of tinnitus for many patients.

Appendix 1 – Follow-up Questionnaire

On the scale below, CIRCLE the number that best describes the loudness of your **usual** tinnitus

| | | | | | | | | | |
|------------|---|---|--------------|---|---|---|-----------|---|----|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Very quiet | | | Intermediate | | | | Very loud | | |

DIRECTIONS: For the questions below, please CIRCLE the number that best describes you

| | Never | Rarely | Sometimes | Usually | Always |
|--|-------|--------|-----------|---------|--------|
| Does your tinnitus | | | | | |
| 1. Make you feel irritable or nervous | 1 | 2 | 3 | 4 | 5 |
| 2. Make you feel tired or stressed | 1 | 2 | 3 | 4 | 5 |
| 3. Make it difficult for you to relax | 1 | 2 | 3 | 4 | 5 |
| 4. Make it uncomfortable to be in a quiet room | 1 | 2 | 3 | 4 | 5 |
| 5. Make it difficult to concentrate | 1 | 2 | 3 | 4 | 5 |
| 6. Make it harder to interact pleasantly with others . . | 1 | 2 | 3 | 4 | 5 |
| 7. Interfere with your <i>required</i> activities (Work, home, care, or other responsibilities) | 1 | 2 | 3 | 4 | 5 |
| 8. Interfere with your social activities or other things you do in your leisure time | 1 | 2 | 3 | 4 | 5 |
| 9. Interfere with your overall enjoyment of life | 1 | 2 | 3 | 4 | 5 |

10 How much of an effort is it for you to **ignore** tinnitus when it is present?

- Can easily ignore it1
- Can ignore it with some effort2
- It takes considerable effort3
- Can never ignore it4

11 How much **discomfort** do you usually experience when your tinnitus is present?

- No discomfort1
- Mild discomfort2
- Moderate discomfort3
- A great deal of discomfort4

12 Does your tinnitus interfere with sleep?

- No1
- Yes, sometimes2
- Yes, often.3

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Developing a structured interview to assess audiological, aetiological and psychological variables of tinnitus

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A new diagnostic instrument, the Structured Tinnitus Interview (STI), is introduced and described in this article. The STI represents a multidisciplinary diagnostic approach whereby major biomedical, audiological and psychological characteristics of tinnitus are assessed in a systematic and standardised form. Separate sections of the instrument cover the patient's tinnitus history, aetiological factors and psychosocial tinnitus-related complaints. Good to excellent test-retest reliability is demonstrated both on item and scale level. The dimensional scales of the STI refer to different areas of psychosocial functioning. They were found to be valid and sensitive to changes induced during cognitive-behavioural treatment.

Introduction

Tinnitus has become a multidisciplinary field of research as well as of clinical practice. Today there is widespread agreement that biomedical, audiological and psychological mechanisms play an important role for the initial development and the subsequent course of this symptom. Since tinnitus can often not be attributed to one single aetiology, large variations are observed regarding its clinical characteristics and the degree of associated personal distress. The specific contributions of somatic and psychosocial factors on the clinical condition may vary according to the stages of the disorder. Modern tinnitus models [1] assume that physiological dysfunctions located in the cochlea or the peripheral auditory system are most crucial for acute forms of tinnitus, whereas psychological factors and central mechanisms of perception and evaluation become increasingly important in chronic cases.

As a consequence, these different dimensions must be considered when tinnitus patients are examined and diagnosed. Although various assessment instruments have been developed in the past, most currently available diagnostic approaches do not consider the multidisciplinary nature of tinnitus, but are restricted to selected areas of symptoms and complaints. From the perspective of methodological quality, only instruments focusing

on psychological characteristics related to tinnitus were standardised and evaluated systematically according to psychometric requirements. One internationally widely used instrument is the Tinnitus Questionnaire [2–4] which has been tested with good results concerning its reliability and validity [5–7].

However, nothing is known until now about the metric quality of medical and audiological findings. Data about tinnitus characteristics such as the location (e.g. ears or head) or the quality and frequency of the sounds (e.g. tonal, intermitting) are reported by many studies, but these descriptions are seldomly assessed in a systematic manner and their reliability has never been tested. Facing this situation, we decided to develop a systematic diagnostic device aiming to include all basic and necessary information for the investigation of single tinnitus patients. This article describes this instrument, the Structured Tinnitus Interview (STI), as well as a study of its test-retest reliability, validity and sensitivity to therapeutic change.

Methods

The Structured Tinnitus Interview (STI)

Since a comprehensive diagnostic examination of chronic tinnitus patients should be based on both self-report and observer-rated findings, we developed the STI to combine these two data sources. The STI was designed for use in routine clinical work as well as for scientific purposes. Our goal was a short but completely structured and

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standardised instrument that would be comprehensive, practical and easy to use. A widely known example (and prototype) of this type of interview is the Structured Diagnostic Interview for DSM-IV [8] which is administered to systematically assess signs and symptoms of mental disorders and determine diagnoses according to fixed decision rules.

The STI consists of 61 items listed on only four pages (a selection of items is displayed in Figure 1). All questions must be read to the patient word by word. Answers are to be coded according to given categories. In order to apply the STI, the clinician or researcher must be familiar with all major clinical aspects of tinnitus including audiological characteristics, aetiological conditions, psychological complications and available treatment options. Therefore, a systematic training is necessary in order to assess patients according to the STI protocol. As the instrument was constructed to reflect our current knowledge about biomedical, audiological and psychological factors contributing to the complex condition of chronic tinnitus, the findings of the complete STI provide a sound basis to develop and discuss treatment strategies with the patient.

The items of the STI are divided up into five consecutive sections:

- 1 Four introductory items refer to *personal data* concerning familial status, profession, current occupational status and level of previous school education.
- 2 The following 14 items summarise major characteristics of the *tinnitus history* such as the location of the noises (left, right, bilateral, in the head), their quality, frequency and temporal pattern, time since onset, form of onset (sudden or progressive), previous changes of loudness, graded subjective maskability, usual constancy or variability of the noises during the course of the day, changes in tinnitus loudness after external acoustical stimulation (especially noise-induced exacerbations), variability of the tinnitus pitch, appraisal of the tinnitus as annoying and distressing, and presence of clinically significant hearing loss according to findings from audiological tests. [Two additional items to screen for vertigo and hyperacusis were included into a later version of the STI.]
- 3 The next section includes 13 items describing *aetiological conditions* the tinnitus could be attributed to. These are: sudden hearing loss, vascular disease, cervical spine dysfunction, craniomandibular dysfunction, acoustic trauma, long-standing exposure to noise, Menière's disease, otosclerosis, acoustic neuroma, central nervous disease, ototoxic substance consumption, family history of tinnitus or ear disease, other aetiological factors (as a residual category). The presence or absence of each condition must be judged by summarising the patient's report and available medical findings. Since simple questions referring to each aetiology are not possible, we included some major diagnostic criteria which may guide the diagnos-

ician through the process of judgement (see examples in Figure 1).

- 4 In the section of *psychosocial aspects of tinnitus*, 26 items describe seven areas: hearing problems related to the tinnitus, intrusiveness of the tinnitus, difficulties with relaxation and sleep, emotional distress, dysfunctional cognition, psychosocial impairment and occupational disability. Most psychological items stem from the TQ for which they had been selected according to factor analysis [4,5]. Each item can be coded on a three-point-scale (two points for 'yes', one point for 'partly/sometimes'). Dimensional scores can be computed for all seven areas as well as for the complete section of psychosocial distress (this score ranges between 0 and 52 points with high scores indicating high levels of psychosocial impairment).
- 5 Three final items summarise information about *previous treatments and their efficacy* as perceived by the patient.

The clinical and psychometric evaluation of the STI

Since its development, the STI has been applied to a large number of inpatients treated in the Roseneck Centre of Behavioural Medicine in Prien, Germany. We developed a systematic treatment programme for patients with chronic tinnitus based on the principles of cognitive-behavioural therapy [9–13]. The Roseneck Centre is a research-oriented hospital affiliated with the Medical Faculty of the University of Munich. Since it is part of the official German tertiary care system, our treatment is open to patients of all levels of social and occupational status. The setting is typically chosen for cases with comorbid physical and psychological symptoms, chronic disorders, and whenever appropriate outpatient treatments are regionally lacking. The STI is used as a tool of standard examination and documentation with each tinnitus patient shortly after admission. It is appreciated as a valuable diagnostic help by our clinicians (psychologists and physicians) and well accepted by nearly all patients. Conducting the STI usually takes about 30 minutes.

To determine the test-retest reliability of the STI, we administered it to examine 65 consecutive patients, twice on two separate occasions, during the first days of treatment. The first (test) diagnostic interview was done by the psychologist or physician who was responsible for the treatment of the individual patient, while the second (retest) interview was performed by an independent clinician (US) trained especially for the purpose of this study. The time interval between both interviews was limited to a maximum of four days in order to avoid discrepancies due to changes of the patients' symptomatology. Since the test and retest interviews had to be independent from each other, there was no discussion among the participating diagnosticians about the comparability of the findings until the complete study was finished. All patients were instructed to give complete information on both occasions and

Items related to tinnitus history (selection).

4. Where exactly do you hear the tinnitus ?

right side (or predominantly right) left side (or predominantly left)

both sides within the head

5. How does the tinnitus sound like ?

Note: First characterized the patient's own description; then let him choose among the options listed below

| Quality of sound: | Frequency range: | Temporal pattern: |
|---|---|-------------------------------------|
| <input type="checkbox"/> tonal | <input type="checkbox"/> low-frequency | <input type="checkbox"/> pulsatile/ |
| <input type="checkbox"/> non-tonal (e.g. buzzing) | <input type="checkbox"/> medium | <input type="checkbox"/> knocking/ |
| <input type="checkbox"/> other quality | <input type="checkbox"/> high-frequency | <input type="checkbox"/> rhythmic |
| | | <input type="checkbox"/> monotonous |

6. When has your tinnitus begun ?

right: _____ left: _____

Please code time since onset:

| | | |
|-------------------|-------------------|---------------------------------|
| 1 = < 1 month | 5 = 2 - 5 years | <input type="checkbox"/> |
| 2 = 1 - 6 months | 6 = 5 - 10 years | left: <input type="checkbox"/> |
| 3 = 6 - 12 months | 7 = 10 - 15 years | right: <input type="checkbox"/> |
| 4 = 1 - 2 years | 8 = > 15 years | |

Items related to tinnitus aetiology (selection).

20. Tinnitus following sudden hearing loss ?

1 = Yes 2 = Probably 3 = No evidence 9 = Unclear

Refer to the following criteria:

- Suddenly occurring hearing loss or sensation of pressure in the ear (temporary or for a longer period) in temporal relationship with the onset or deterioration of the tinnitus

21. Tinnitus following vascular disease ?

1 = Yes 2 = Probably 3 = No evidence 9 = Unclear

Refer to the following criteria:

- History of cerebral ischemia (e.g., stroke, TIA, pathological findings in doppler sonography or angiography)

22. Tinnitus following disorders of the cervical spine ("cervicogenic tinnitus") ?

1 = Yes 2 = Probably 3 = No evidence 9 = Unclear

Refer to the following criteria:

- Loudness of tinnitus changes when neck is turned around or stretched (see examination A)
- Whiplash injury of the cervical spine (e.g., after car accident) directly before onset or deterioration of the tinnitus
- Tinnitus loudness is often fluctuating

Items related to psychological and psychosocial tinnitus distress (selection).

34. Does the tinnitus make it more difficult to listen to several people at once ?

No partly/ sometimes Yes

40. Does the tinnitus affect your concentration ?

No partly/ sometimes Yes

43. Does it take you longer to get to sleep because of the tinnitus ?

No partly/ sometimes Yes

49. Are you more irritable because of the tinnitus ?

No partly/ sometimes Yes

53. Do you think that your life will not be worth living if the tinnitus would continue ?

No partly/ sometimes Yes

Figure 1 Examples from the Structured Tinnitus Interview (STI) [the STI is available from the authors of this report]

not to regard the second interview as a continuation of the first. 23 patients of the sample were male and 42 were female. Their mean age was 46.8 years (sd = 9.9) and the age ranged between 16 and 75 years. Of the initial sample, 57 patients could be examined once again shortly before discharge four to eight weeks later (four patients refused this third examination because of time restrictions, three had left the hospital because of acute therapeutic problems and one patient had changed to another department because of other than tinnitus-related psychological symptoms).

Results

We used the kappa statistic to analyse the categorical data of the test-retest study and Pearson correlation coefficients for the dimensional scales of

tinnitus-related psychosocial complaints. Table 1 summarises the kappa values for all single items of the STI. It should be considered for an adequate interpretation of the kappa statistic that values of >0.70 are conventionally regarded as excellent, values between 0.50 and 0.70 as acceptable and values <0.50 as insufficient [14]. Unlike correlation coefficients, kappa takes chance agreements between independent raters into account and usually varies between 0 and 1.0 (kappa is 1.0 if perfect diagnostic congruence was reached).

We obtained good to excellent test-retest reliabilities for about 80% of the STI items from the sections of tinnitus history, aetiology, and psychosocial aspects related to tinnitus. As can be seen from Table 1, characteristics such as the location of the tinnitus, aspects of its quality and temporal pattern, the time since onset, tinnitus maskability and the presence of high-frequency hearing loss were

Table 1 Test-retest reliability of the STI items

| Kappa | Tinnitus history |
|-------|---|
| >0.70 | Location of tinnitus left, right or bilateral Quality of tinnitus sound described as non-tonal (e.g. buzzing) Temporal pattern of tinnitus described as monotonous Time since onset of tinnitus >6 months or >12 months Type of tinnitus onset described as suddenly or slowly progressive Tinnitus described as always or never masked by external sounds Tinnitus described as being permanently present Hearing loss found to be definitely present Type of hearing loss described as >30dB above 3,000 Hz |
| ≥0.50 | Frequency of tinnitus described as low, medium or high Temporal pattern of tinnitus described as pulsatile/knocking/rhythmic Development of tinnitus loudness in the past Tinnitus described as can sometimes be masked by external sounds Loud external noise reported to cause tinnitus exacerbation Occurrence of tinnitus-free intervals reported Subjective description of tinnitus as annoying Type of hearing loss described as >20dB below 3,000 Hz |
| <0.50 | Location of tinnitus described as within the head Quality of tinnitus sound described as tonal (or other rare descriptions) Descriptions of daily fluctuations of tinnitus loudness and frequency |
| | Tinnitus aetiology |
| >0.70 | Sudden hearing loss, cervical spine dysfunction, craniomandibular dysfunction, long-standing noise exposure, Menière's disease, otosclerosis, acoustic neuroma |
| ≥0.50 | Acoustic trauma, ototoxic substance intake, hereditary |
| <0.50 | Vascular dysfunction, neurological disease |
| | Psychosocial aspects associated with tinnitus |
| >0.70 | Voices of others sound distorted, localisation of external sounds unclear, problems falling asleep, wakes up during the night, feels afraid of being seriously ill, has more everyday stress, feels weary of life, has lost friends, interpersonal relationships impaired, more days unable to work |
| ≥0.50 | Conversations disturbed, difficulties when telephoning, all day long aware of tinnitus, can't ignore tinnitus, concentration impaired, difficult to listen to music or watch TV, wakes up earlier in the morning, attributes all problems to tinnitus, sees tinnitus as the major problem in life, has fewer social activities, avoids arguing with others, functioning at work decreased, wants or has already received premature retirement |
| <0.50 | Feels tense, feels sad and depressed, feels more irritable, feels loss of control |

Kappa >0.70 excellent; ≥0.50 acceptable; <0.50 insufficient

diagnosed with an excellent level of objectivity and reproducibility. Similar results were found for the aetiological factors of sudden hearing loss, cervical spine dysfunction, craniomandibular dysfunction, long-standing noise exposure, Menière’s disease, otosclerosis and acoustic neuroma. In the section of psychosocial aspects, a large number of items describing hearing problems, difficulties of relaxation and sleep, emotional distress and psychosocial or occupational impairment had kappa values of 0.70 or higher. However, Table 1 also shows that some items were problematic because of insufficient reliability values. These were mainly the description of tinnitus being localised ‘in the head’, tonal descriptions of the sound, reports about usual daily fluctuations of loudness as well as frequency of the noises, vascular and neurological diseases as possible causes of the tinnitus, and also four psychological items describing negative feelings as related to the subjective tinnitus experience. Therefore, this information should be interpreted only with great care if reported by the patients or if judged on the basis of previous medical and audiological examinations.

The dimensional scale reliabilities from the psychosocial section are listed in Table 2. Each scale consists of four items except for the occupational impairment scale which consists of only two items. Since the maximum score on item level is 2 points, no more than 8 points can be reached for each scale (no more than 4 points for occupational impairment). The STI global score is computed by summing up all scales (maximum of 52 points). All values except for emotional distress and dysfunctional cognition were ≥0.80. The reliability for the STI global score was as high as 0.90. In all, these results indicate a high and satisfying reliability of the STI measures of psychosocial tinnitus-related distress, especially if one considers that the number of items within each scale is relatively small.

To evaluate the validity of the STI, we compared its scales with those of the TQ. Since the TQ has been evaluated psychometrically in several studies [2,3], it can be regarded as a valid criterion. TQ data were available from 51 patients of our sample described above. The intercorrelation matrix between the STI and TQ scales is shown in Table 3.

Table 2 Test-retest reliability of the STI scales describing tinnitus-related psychosocial distress

| STI scales | Pearson correlations |
|--|----------------------|
| Auditory perceptual difficulties | 0.84 |
| Intrusiveness of the tinnitus | 0.85 |
| Difficulties with relaxation and sleep | 0.84 |
| Emotional distress | 0.79 |
| Dysfunction cognition | 0.79 |
| Psychosocial impairment | 0.81 |
| Occupational impairment | 0.84 |
| STI total | 0.90 |

It can be seen that corresponding scales of both instruments showed good congruence (bolded values) and the total scores had a high correlation of 0.80. It should be noted, however, that both instruments are not identical in their contents despite some obviously similar scales. For example, scales of psychosocial and occupation impairment can be found only in the STI. Previous analyses of the TQ had shown that items covering these areas were underrepresented; therefore, corresponding scales had not been identified through factor analysis [5].

In a last step, we evaluated whether the STI is sensitive to changes in psychosocial symptomatology during the course of inpatient cognitive-behavioural treatment. We compared the findings at admission and shortly before discharge from our hospital for a sample of 51 patients. The efficacy of our treatment programme has already been demonstrated in previous studies [8–12]. Table 4 shows that significant reductions were found for five of the seven STI scales as well as for the STI total score. The magnitude of these effects are comparable with those found by means of the TQ. We can therefore conclude that the STI is able to assess such changes of acute tinnitus-related psychosocial distress.

Discussion and conclusion

Recent tinnitus research has emphasised the complex interaction of biomedical, audiological and psychosocial factors, especially for the development

Table 3 Correlations between STI and TQ scales

| | TQ-E | TQ-C | TQ-E + C | TQ-I | TQ-A | TQ-SI | TQ-So | TQ total |
|-----------|-------------|-------------|----------|-------------|-------------|-------------|-------|-------------|
| STI-A | 0.39 | 0.29 | 0.36 | 0.37 | 0.73 | 0.10 | 0.26 | 0.47 |
| STI-I | 0.65 | 0.48 | 0.60 | 0.76 | 0.65 | 0.36 | 0.38 | 0.73 |
| STI-RS | 0.57 | 0.51 | 0.57 | 0.59 | 0.32 | 0.87 | 0.18 | 0.66 |
| STI-E | 0.62 | 0.46 | 0.58 | 0.47 | 0.47 | 0.36 | 0.33 | 0.60 |
| STI-DC | 0.59 | 0.51 | 0.58 | 0.49 | 0.39 | 0.27 | 0.23 | 0.57 |
| STI-P | 0.59 | 0.28 | 0.47 | 0.44 | 0.63 | 0.08 | 0.26 | 0.52 |
| STI-O | 0.49 | 0.24 | 0.40 | 0.31 | 0.40 | 0.15 | 0.35 | 0.43 |
| STI total | 0.78 | 0.55 | 0.71 | 0.69 | 0.73 | 0.44 | 0.39 | 0.80 |

TQ scales: E = Emotional distress; C = Cognitive distress; E + C = Emotional and cognitive distress; A = Auditory perceptual difficulties; SI = Sleep disturbances; So = Somatic complaints

STI scales: A = Auditory perceptual difficulties; I = Intrusiveness of the tinnitus; RS = Difficulties with relaxation and sleep; E = Emotional distress; DC = Dysfunctional cognition; P = Psychosocial impairment; O = Occupational impairment

Table 4 Measuring therapeutic change by means of the STI

| | Admission | Discharge | Significance |
|-----------|---------------|---------------|--------------|
| STI-A | 3.49 (2.56) | 2.95 (2.41) | p < 0.01 |
| STI-I | 4.65 (2.36) | 3.84 (2.48) | p < 0.01 |
| STI-RS | 4.33 (2.45) | 3.77 (2.59) | n.s. |
| STI-E | 4.56 (2.04) | 3.00 (2.10) | p < 0.01 |
| STI-DC | 2.93 (2.24) | 1.68 (1.97) | p < 0.01 |
| STI-P | 3.26 (2.71) | 2.24 (2.29) | n.s. |
| STI-O | 2.42 (1.60) | 2.23 (1.55) | p < 0.01 |
| STI total | 25.60 (11.60) | 19.70 (12.10) | |

STI scales: A = Auditory perceptual difficulties; I = Intrusiveness of the tinnitus; RS = Difficulties with relaxation and sleep; E = Emotional distress; DC = Dysfunctional cognition; P = Psychosocial impairment; O = Occupational impairment
Significance of change tested with Student's t test, one-tailed

of chronic forms of tinnitus [1]. We therefore felt that a comprehensive and standardised instrument to assess these different facets of the tinnitus condition is needed. Although many previous studies have assessed medical and acoustical characteristics in tinnitus patients, nothing was known about the metric properties of such measures. Systematic psychometric investigations had been reported only for questionnaires focusing on psychological tinnitus-related aspects. In this article, we described the Structured Tinnitus Interview (STI) as a new approach which allows a more complete examination of the tinnitus patient. Unlike questionnaires, the STI allows for ratings and judgements of the clinician based on different sources of information. In addition, since the patient is systematically asked about the impact of the tinnitus on his psychosocial life, the clinician can get a clearer idea about necessary and useful treatment options.

In this paper we presented data about the interview's test-retest reliability, validity and sensitivity to changes in symptomatology. It was demonstrated that the majority of the items and all scales had good stability when patients were investigated by different and independent diagnosticians. Furthermore, there was good congruence with the scales of the well validated TQ and treatment-induced changes were significantly reflected in all except two STI scales.

We can therefore conclude that the STI is suitable to be used both for clinical and research purposes. Our experience from the examination of numerous patients clearly shows that the interview is very well accepted by both clinicians and patients. We have used this instrument with hundreds of tinnitus patients as a routine diagnostic standard. It can serve as a valuable tool for standardised diagnostics, documentation and treatment planning. From a scientific point of view we feel that the approach described in our study could enhance the international comparability of findings from different groups.

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Psychiatric profile of tinnitus patients referred to an audiological clinic

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Introduction

Although tinnitus is a common symptom in the population, the occurrence is higher in patients with hearing loss [1,2]. Interestingly, 94% of normal hearing volunteers could experience tinnitus in complete silence [3]. However, the hearing parameters have no strong impact on the severity of the sufferings related to tinnitus and stronger predictors to the severity of tinnitus are to be found among psychological factors [4–17]. The importance of psychological, audiological factors and general health to the sufferings of tinnitus has recently been reviewed by Holgers *et al.* 1999 [18].

Hazell and Jastreboff [19] introduced the terminology “emergence of tinnitus” and “persistence of tinnitus”. They proposed that persistent tinnitus could be regarded as a conditioned response to the perceived tinnitus sound, which involves both the limbic as well as the autonomic nervous system and the tinnitus retraining therapy (TRT) they have developed is aimed to decrease this response.

Important issues are to identify and treat the etiological mechanisms behind the development from emerged tinnitus to persistent severe tinnitus. We have recently described predictive factors for tinnitus severity, measured by long-term absence from work related to tinnitus. The main predictors were depression profile in the Nottingham Health Profile (NHP), reduced general health and hearing impairment. The tinnitus-patients with reduced general health as a contributing factor for the severity of tinnitus did also score high on the psychological part of the tinnitus severity questionnaire (TSQ) [18].

The aim of the present study was to investigate psychiatric parameters in consecutive tinnitus patients without severe hearing impairments to avoid psychological biases by social isolation secondary to hearing loss.

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Patients

All patients who had been referred to an audiological physician at the audiological clinic due to tinnitus with pure tone thresholds in low, mid or high frequencies better than 50 dBHL during a 6 months period were included in the study. A total of 98 patients were included in the study group (33 women and 65 men). Eighty-two patients (30 women and 52 men) fulfilled the assessment and 16 patients were dropouts.

Methods

All 96 patients were invited to the audiological department for follow-up 24 months after the first visit to the clinic. Onset and circumstances for tinnitus debut were investigated in open questions as well as the present severity of tinnitus.

A 90-minute assessment conducted by an experienced psychiatric specialist was performed. A standardised diagnostic interview (SCID-P) for multiaxial psychiatric diagnostics in accordance with the Diagnostic and Statistical Manual of Mental Disorders (DSM-III R) system (27) was utilised and the results of axis I-II will be presented. Hospital Anxiety and Depression Scale (HAD-S), which is a self-administered scale with subscales for anxiety and depression graded for severity-measuring was also used.

Results

Tinnitus symptoms

The patients described the present symptoms of tinnitus 24 months after the first tinnitus consultation as follows: 17% did not perceive tinnitus any more, 4% said that they seldom think of their tinnitus, 39% did not experience tinnitus, unless they felt lonely or depressed; unless it was quiet or when someone talked about tinnitus, 33% said that tinnitus is always severe and 5% told that it was difficult to think about anything than tinnitus. The remaining 2% did not give any conclusive answer.

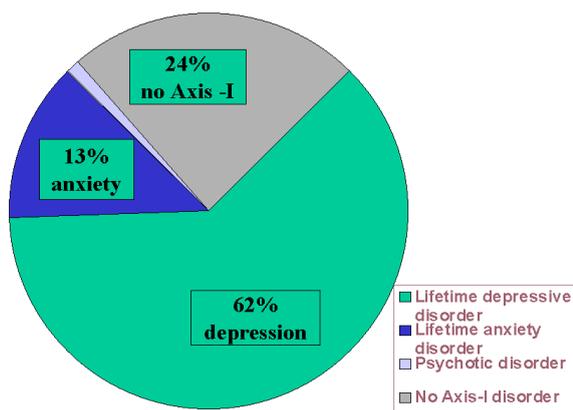


Figure 1

The standardised diagnostic interview axis I

Depressive disorders: In 62% of the patients signs of lifetime depressive illness occurred and 39% had current depression at the time for the investigation. In Table 1 the anamnestic depressive disorders and the numbers of patients are presented at the time for the investigation.

Table 1

| Depressive disorders | Patients |
|-----------------------------|----------|
| Dysthymic disorders | 4 |
| Mild | 3 |
| Moderate, recurrent | 18 |
| Moderate, single episode | 8 |
| Moderate, chronic | 8 |
| Moderate, partial remission | 5 |
| Severe, single episode | 2 |
| Severe, chronic | 2 |
| Bipolar, (depression) | 1 |

Anxiety disorders: In additional 13% patients anxiety spectrum disorders such as social phobia, panic syndrome, generalized anxiety disorder, obsessive-compulsive disorder and somatization or somatoform pain syndrome were classified.

Specific phobias are not included. If there were more than one diagnoses in each patient, only the most disabling diagnose is included.

Depressive and anxiety disorders: In the 25 (30%) cases where the patient exhibited depressive illness as well as anxiety, we have only reported the depression-related diagnosis, and specific phobias were not included. Fifty per cent of the patients with depression also suffered from chronic anxiety disorder.

Fifty-five of the patients already suffered from depression and/or anxiety disorder before the onset of tinnitus. In 90% of the patients with depressive or anxiety disorders, the onset of these disorders happened before or together with the onset of tinnitus.

Other or no symptoms on axis I: One patient had chronic psychotic disorder and 16 patients had no diagnose on axis I.

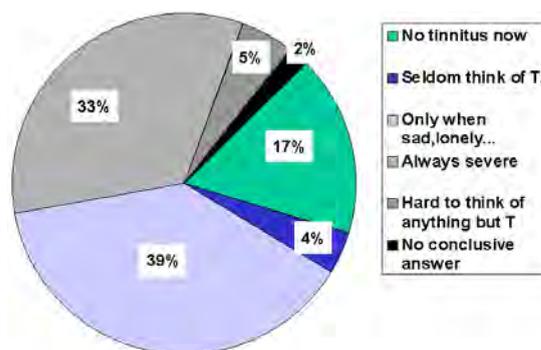


Figure 2

SCID-P Personality

Preliminary diagnoses: Cluster A (for example: paranoid or schizoid personality traits) was noted in 2 patients, cluster B (for example: antisocial or borderline personality traits) in 3 patients and cluster C (for example: phobic, dependent or obsessive-compulsive personality traits) in 50 patients.

Discussion and conclusion

The occurrence of depressive and anxiety-related syndromes in tinnitus patients were remarkably high (62/80 patients) in the present study. These symptoms also covaried with tinnitus. This is in accordance with a study including 24 consecutive tinnitus patients and 14 controls in which, the tinnitus patients were reported to have significantly greater lifetime prevalence and of major depression (62% vs. 21%) as well as current depression (48% vs. 7%) than the controls [20].

Another important finding from the present study was that in 90% of the tinnitus patients with depression and/or anxiety disorders the psychiatric disorder had started before or at the same time as the onset of tinnitus. It is often claimed that depression is secondary to tinnitus, but our results indicate that tinnitus is secondary or parallel in time to depression or anxiety disorders. There is a dysfunction or vulnerability in the serotonergic system during depression and maybe some of the anxiety syndromes. Since it has been reported that serotonin is involved in the modulation of sensory processing in the primary auditory cortex [21,22] it is possible that due to the dysfunction in the serotonergic system during depression, the awareness of tinnitus increases.

We have earlier shown that depression profile in the NHP is a strong predictor to the severity of tinnitus and this factor can be identified by a screening procedure at the first visit to the clinic. We underline the importance of early identification of depression or anxiety disorders within the tinnitus patient [18].

With an effective and early intervention against the depressive disorder as such the long term prognosis for the depressive patient is better [23–26]. Since psychological factors are known to enhance tinnitus suffering, early identification and treatment

of these symptoms can be of crucial importance to avoid the process from emergence of tinnitus to tinnitus with severe impact on the daily activity and quality of life.

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The Swiss concept I: Tinnitus rehabilitation by retraining

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Tinnitus retraining differs from other therapeutical approaches in so far as it does not aim at an extinction of the tinnitus. The term rehabilitation is more appropriate than the term therapy: tinnitus fulfills the WHO requirements of a handicap and necessitates rehabilitation. The Swiss concept [1] definitely bases on the principles and rules of TRT, but it includes supplementary rehabilitation measures on the biological, psychological and social level. The Swiss approach is more holistic than a mere TRT and matches perfectly the actual principles of psychosomatic medicine. In contrast to the TRT, the Swiss concept includes *all* tinnitus patients – even those who are not suited for TRT. Therefore our experiences reflect an *unselected* sample of tinnitus sufferers.

Our rehabilitation programm consists of (1) counselling, (2) silence avoidance and (3) any measures suited for improvements of the general well-being in order to minimize negative lateral influences leading to an apparent amplification of tinnitus perception. The rehabilitation team decides, what measures seem to be necessary for each individual patient. Proper counselling is done, using a simple computer model of tinnitus perception. Tinnitus loudness, as it is measured after pitch matching, never increases and normally not exceeds 15 dB SL. This applies even to cases, where a new inner ear damage with apparent loudness increase occurred. The subjective variations of tinnitus loudness solely depend on lateral negative factors such as stress, fatigue, noise, depression, anxiety, pain, common colds or social problems. Silence avoidance is planned according the TRT rules. Hearing aids or noise generators as well as soft background noise levels (water noises are the first choice) are used. The duration of the rehabilitation program depends on the individual needs. Preliminary results of a sample of 120 unselected patients are presented. The mean observation time was 7 months. Improvement was defined as a significant improvement of the main items of the Jastreboff questionnaire. The overall rate of improvement was 71%. Superior results were obtained in early cases (tinnitus duration less than 1 year), in the age group below 20 years, and after supplementary holistic body work. Significantly low rates of improvement were found in cases after severe traumatic brain damage and/or whiplash injury, in cases where the insurance problems remained unsolved, and in unemployed people.

Tinnitus Rehabilitation by Retraining

For some tinnitus sufferers, the cognitive approach by counselling, combined with silence avoidance, is sufficient. For severe cases, however, a broader approach is needed. It includes any means that could improve the general well being, in order to minimize lateral influences inducing an amplification of the subjective tinnitus loudness. For counselling purposes, a simple computer model [1] has proven effective. It fits perfectly into the tinnitus sufferer's personal experience even when the patient is not familiar with the computer world: the input of data through our sensory organs exceeds the capacity of our conscious perception by a factor of nearly one million. Conscious perception is the end product of a highly selective data processing. Only the most important information has got a chance to

be perceived consciously. Although it is caused by a (sometimes astonishingly small) inner ear lesion, tinnitus has to be regarded a jamming program within the subcortical software. Measured by tinnitometry, the loudness of this jamming program remains stable – even after a new inner ear damage. It can be concluded, that tinnitometry measures tinnitus on a subcortical level, disregarding the variations of the conscious tinnitus sensation. Negative lateral influences such as stress, fatigue, depression, anxiety, common colds, pain and noise can switch on a subcortical amplifier, whose activity variations are reflected by considerable variations of the subjective loudness sensation. Vicious circles further increase the loudness: lack of sleep increases the fatigue, which in turn promotes further amplification. Tinnitus rehabilitation aims at changing the subcortical significance of the tinnitus by active and passive retraining. Counselling induces active retraining, and silence avoidance is used for passive

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retraining. Hearing aids or noise generators are fitted according the TRT principles, and soft background noise (water noises are preferred) are recommended, especially for the bedrooms.

The third pillar of our concept includes means to improve the general well being of the patient. Somatic, psychological and social problems have to be cared for. Improvement of sleeping disorders and depression is of prime importance. Futile attempts to cure the tinnitus are strictly avoided. They lead to chronification of the tinnitus. In order to overcome tinnitus, tinnitus sufferers have to undergo a personal evolutionary process. Therefore supporting process-inducing therapies (psychotherapy or body work) are an excellent extension of TRT.

Results

Two hundred and fifteen unselected consecutive patients were evaluated. In most cases, the rehabilitation program ist still going on. The mean observation time was 9.7 months (in 75% less than 1 year), the mean number of consultations was 3.6. The age distribution shows a peak from 20 to 65 years, thus corresponding to the active period of professional work. Improvement was defined as a

significant improvement in at least two measurable parameters of the quality of life such as sleep, panic attacks, resumption of given up activities, improvement of depression, noise tolerance, long pauses of conscious tinnitus perception). The overall rate of improvement was 71%, 29% remained unchanged. Significantly better results were obtained in cases with short tinnitus duration (less than 1 year), in the age group below 20 years, and in cases with additional body work, together with intense counselling. Significantly worse were the results in cases with insurance claims, incapacitating problems beside the tinnitus, and in unemployed people. High grade deafness, age above 70 years and tinnitus duration of more than 5 years also lowered the success rate significantly. The use of noise generators, psychotherapy, antidepressive drugs, the length of the observation time, the tinnitus pitch as well as the tinnitus loudness match did not influence the results.

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Controversies between cognitive therapies and TRT counseling

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The neurophysiological model of tinnitus postulates that various parts of the brain, in addition to the auditory system, are involved in clinically-relevant tinnitus, with emphases on connections between the auditory, limbic and autonomic nervous systems (ANS). Two loops can be distinguished: high level cortical, involving conscious verbalization and beliefs, and the other subconscious, nonverbal. In the majority of cases the lower, subconscious loop is dominant, with the activation of limbic and ANS occurring on the conditioned reflexes principle. The higher, conscious loop can modulate the lower one, but its blockage typically is not sufficient for removing tinnitus as a problem and for its habituation.

Counseling in TRT is a teaching session, aimed at providing patients with a new frame of reference by explaining potential mechanisms of tinnitus generation, neurophysiological mechanisms through which tinnitus is influencing various aspects of their lives, and that by activating a naturally occurring mechanism of brain function (habituation and underlying it plasticity), it is possible to achieve primary habituation of the tinnitus-induced reaction of the brain and the body, and secondary of tinnitus perception. The clear goal of achieving an active and selective block of tinnitus-induced reactions is set for the patients.

Cognitive therapies are predominantly aimed at improving coping skills, acting through changes of specific beliefs, which have to be identified. As such, when successful in some patients with a dominant upper loop, cognitive therapies are typically unable to provide long-lasting effects because they are not sufficiently helpful in modification of the lower loop. Moreover, a frequent approach in cognitive therapies involves the therapist's belief that the tinnitus problem results from psychological or psychiatric abnormalities.

Contrary to this approach, the neurophysiological model of tinnitus postulates that tinnitus become a problem due to evoking a proper reaction to an improper stimulus. Compensation within the auditory system contributes to, or is responsible for, providing tinnitus-related neuronal activity. The limbic and ANS are frequently within the norm but their reflex-based reactions occur to a stimulus which should not cause their activation.

Notably, while we believe that TRT is optimal for the majority of patients, we are not postulating that TRT is the only method for treating tinnitus. A variety of other methods can be used. Moreover, while not as effective as the full method, even partial implementation of TRT can provide help for some patients. Only well designed, research quality studies, will provide proper evaluation of various approaches for treatment of tinnitus and hyperacusis.

“Tinnitus is a common symptom, but a problem only for some people.”

This statement is well known to those who are trying to bring help to patients afflicted by tinnitus. The obvious question, which arises from this sentence, is what causes tinnitus to go from a non-bothering experience to become a severe problem for some people. Analyses of the most common complaints reported by tinnitus patients, such as sleep disturbances, problems with concentration, distress, anxiety, depression, inability to enjoy activ-

ities in life, and general classification of these problems such as emotional, social, communication issues, led to the conclusion that the response of the people to the tinnitus signal is what starts the problems, and initiates the vicious circle. The speed and the degree in which this vicious circle develops are influenced by personality, emotional status (i.e., the level of distress), life style (i.e., how busy the person is), individual perception of the problem, general health issues, hearing problems, sound sensitivity, etc. Consequently, detailed analyses of the factors responsible for the difficulties experienced by individual tinnitus patients have to be performed. These analyses would allow us to recognize elements caus-

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ing or maintaining tinnitus-related distress, and help to design strategies in an attempt to deal with the problematic event or situation [1–3].

The goal of the treatment, based on the above assumptions, is to remove the distress and other psychological and physiological effects of distress, teach coping strategies and by this, change the perception of tinnitus and help patients to learn to live with the tinnitus, in a positive manner of this phrase. This is the basis for cognitive-behavioral therapies, which are predominantly aimed at improving coping skills, changing beliefs, and in this way, acting at the cortical level involving conscious verbalization.

These therapies aim to help identify the thoughts, worries and beliefs and then challenge them, discuss and replace with more positive. They are aimed at modifying the perception, emotions, and attention of the patients and correct the way that they respond to the presence of tinnitus [1–3].

Tinnitus Retraining Therapy (TRT) is based on the principle that abnormal sustained activation of the limbic and sympathetic autonomic nervous systems is responsible for the tinnitus-induced distress and successively for the bothersome clinically important tinnitus [4–7]. But it does not exclusively focus on cognitive elements, or even consider them as crucial, during the treatment. When negative thoughts or beliefs are expressed by patients, rather than demanding cognitive sessions in close contact with the therapist, the explanation, based on our knowledge of how the central nervous system functions, auditory system, and potential mechanisms of tinnitus, as well as discussions of the audiological and medical evaluations, are offered to the patients. Tinnitus is presented as resulting from compensatory, positive activity within the auditory system, and a response of the system to small distortions. Discussion of tinnitus as a neutral signal, rather than challenging an individual's thoughts or beliefs, is part of the initial contact with the patient.

Surprisingly, a majority of the patients can link their tinnitus to some emotional stress or discomfort as a triggering factor. This temporal association of an irrelevant distressing event (e.g., divorce, retirement) with the noticed perception of tinnitus causes very strong association, and create a conditioned reflex linking tinnitus signal with distress, which results in producing a reaction of distress in response to the presence of the tinnitus signal. The constant presence of tinnitus, accompanied by feeling of distress, reinforces and enhances this reflex.

In the remaining minority of people afflicted by tinnitus, who are not able to associate an onset of tinnitus with any particular event, the distress might result from non-recognized changes of the body function (e.g., fluctuation in hormone levels), which influence the status of well being or the fluctuation of tinnitus intensity. It is well established, that one does not have to know exactly what is causing discomfort to feel uncomfortable.

It is possible to attenuate unpleasant reaction and to decrease the magnitude of negative association by means of passive extinction, acting at subconscious

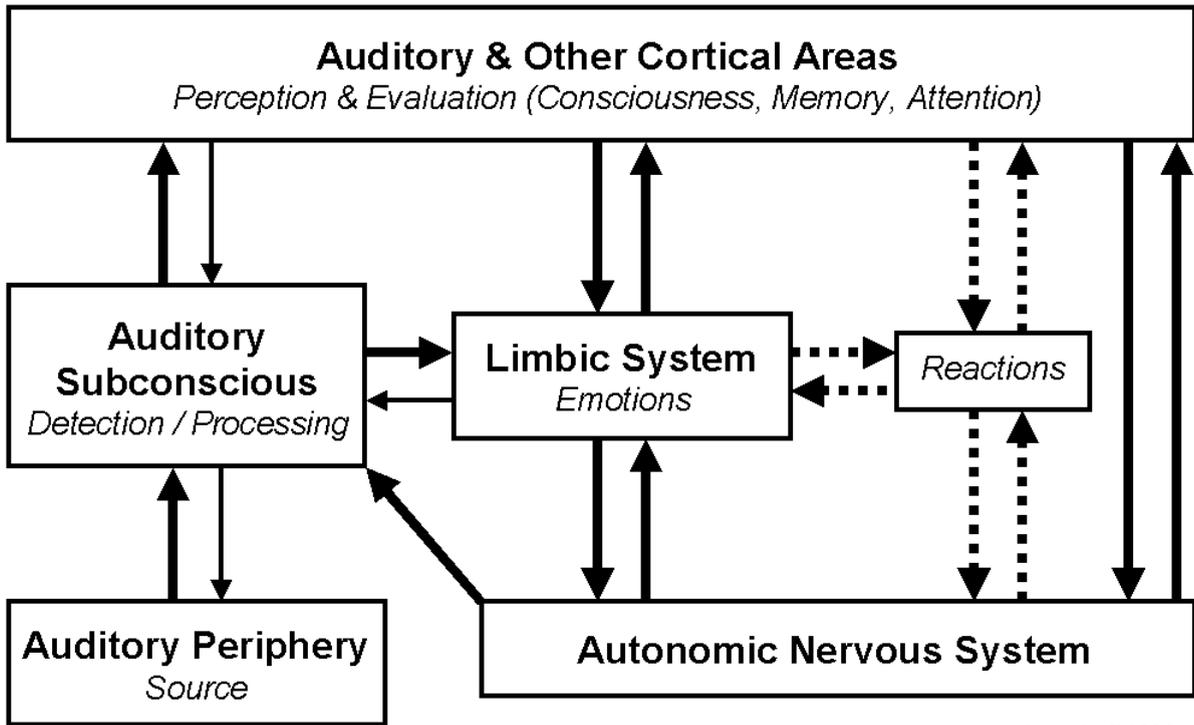
level. Ideally, passive extinction will occur if tinnitus is no longer classified as having negative connotations or being associated with a danger, and if its presence is no longer accompanied by distress. The passive extinction can occur, as well when some distress is still present, but it is decreased. This decrease could be accomplished by providing patients with an explanation, discussion about sound and its proper use (changing activation of high cortical areas), and by actual use of the sound to increase background neuronal activity and effectively decrease the activation of the limbic and autonomic nervous systems (changing the activation in all systems).

The general outline of the neurophysiological model is presented in Figure 1.

Although cognitive theory and the neurophysiological model of tinnitus agree in regard to the involvement of the higher level of cortical parts (higher loop), in the interpretation of the tinnitus signal, the neurophysiological model and TRT are focusing very distinctively on subconscious, non-verbal processing (lower loop). The higher, conscious loop can modulate the lower loop, but typically its blockage is not sufficient for removing tinnitus as a problem and for sustained, permanent habituation. The neurophysiological model and the treatment based on it consider, in addition to the cortical parts, connections among auditory, limbic, and autonomic nervous systems, and recognize the need to modulate and/or change connections by acting at all levels to induce and sustain plastic changes in the central nervous system. In most cases, modifications of the higher loop are not sufficiently helpful to create changes of the lower loop and in providing long-lasting effects. Figures 2 and 3 are showing the main sites of action of cognitive therapies and TRT according to the neurophysiological model.

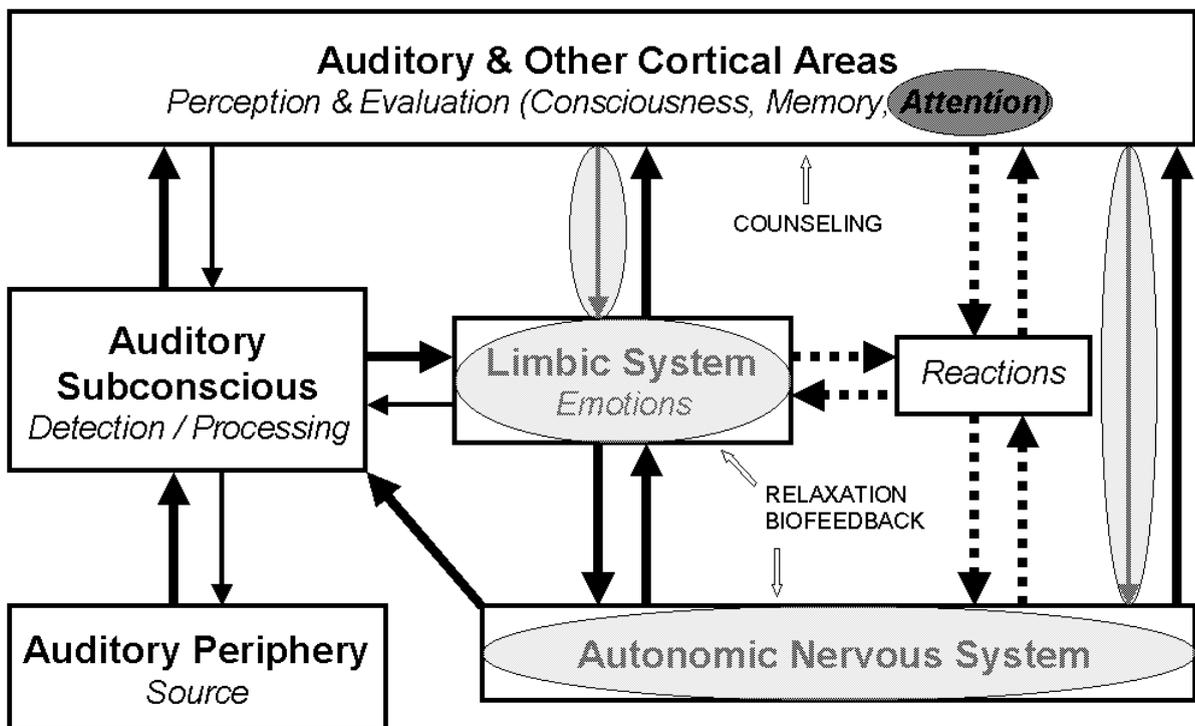
TRT can be named Habituation Sound Therapy (HST). One-on-one interaction, focusing on problems of an individual patient, teaching and providing in a straightforward manner information during sessions, conventionally called directive counseling, and a specific use of sound are always included in TRT. Whereas, for many tinnitus patients, instruments are not an indispensable part of TRT, the use of sound is. Consequently, a counseling session always includes discussion and instruction on the proper use of sound. TRT counseling is a teaching session, aimed at providing patient with a new frame of reference by explaining potential mechanisms though which tinnitus influences the various aspects of their life, and that by activating a naturally-occurring mechanism of brain function (habituation and underlying it, plasticity), it is possible to achieve the primary goal of habituation of the tinnitus-induced reactions of the brain and body and the secondary goal of tinnitus perception. These goals and their justification are clearly presented to the patients.

Patients are presented with the concept of tinnitus developed as a conditioned reflex yielding a proper reaction to an improper stimulus. Positive compensatory action within the auditory system



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Figure 1 The outline of the neurophysiological model of tinnitus. Thickness of lines represents relative strength of a given connection, and going through this connection tinnitus-specific neuronal activity. Note, that all systems are highly nonlinear, and connected as a dynamic network.



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Figure 2 Primary sites and mechanisms of action of cognitive therapies. Light ovals represent changes yielding the improvement; dark – worsening. The change of line thickness, as compared with Figure 1, indicate presumable change of activation and of a connection weight.

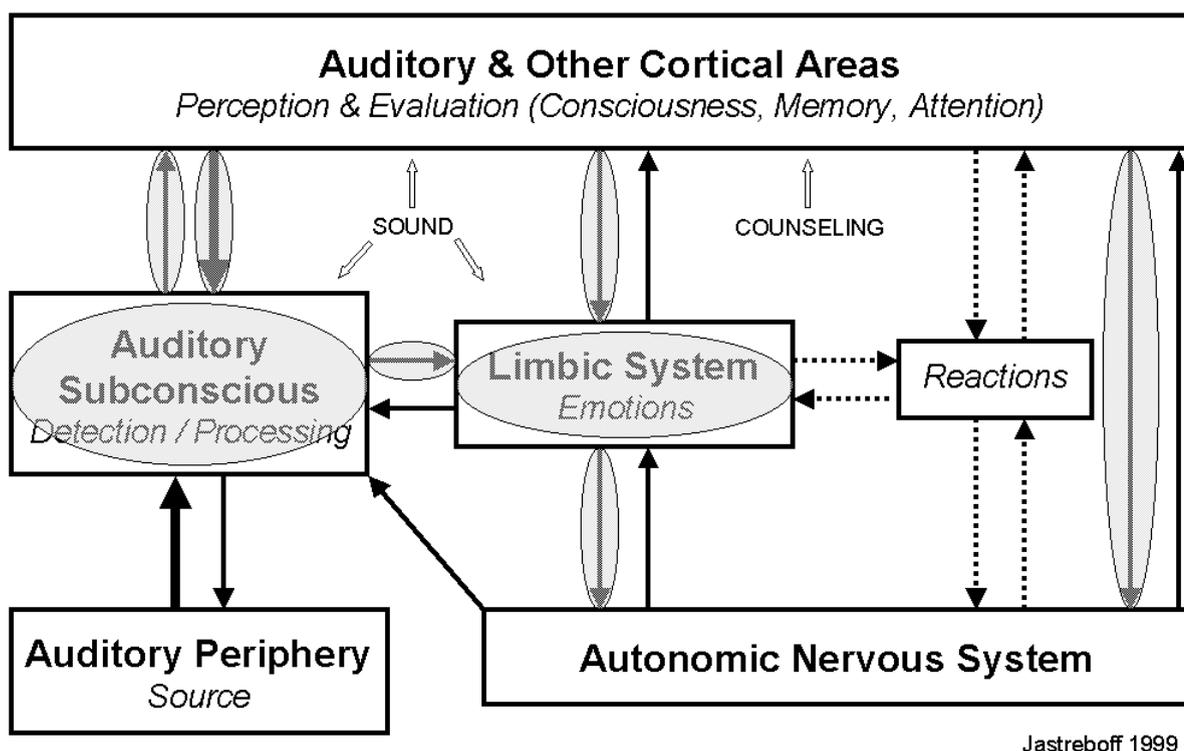


Figure 3 Primary sites of action and mechanisms of action of TRT.

contributes to, or is responsible for, providing the tinnitus-related neuronal activity. The limbic and autonomic nervous systems are frequently acting within the norm before tinnitus, but their reflex-based reactions occur to a stimulus which should not cause their activation.

TRT counseling is using elements of cognition, but it is not, and never was, intended to be strictly cognitive, collaborative therapy, where the patients and therapist engage in the process, usually time consuming, of identifying, challenging the dysfunctional thoughts, and then replacing them with idiosyncratic constructive responses, or teaching a different attention or relaxation techniques (e.g., use of music for relaxation or distributing sounds to influence emotions and/or perception) simply to change a patient's perception, attention and emotions toward tinnitus (influencing an upper loop), to improve a person's well-being, everyday life, social interaction and work abilities, in spite of tinnitus.

TRT counseling is interactive (questions/answers) and directive, where the "counselor introduces information, content or attitudes not previously expressed by the client" [8]. It is not our goal to challenge the patient's beliefs, particularly when a patient is not forceful in discussing them. This is why, in most cases, very frequent visits are not needed. With additional information about the problems discussed at the first visit provided to the patients in take-home written materials, it is sufficient to schedule follow up visits initially once a month, and later during the treatment, once every several months. To assure that proper contact is maintained, patients are always encouraged to call with any questions and concerns at any point of the therapy.

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Results of tinnitus retraining therapy

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A retrospective study of 483 patients were offered Tinnitus Retraining Therapy (TRT) based on the Jastreboff neurophysiological model, at the London Tinnitus and Hyperacusis Centre. 381 attended at 6–12 months and of these 224 attended a final appointment, over a median period of 21 months. Of the 224 patients receiving full TRT, 83.7% achieved a significant benefit using the 40% improvement criteria. The group that did not reach this significance level did however show a beneficial change in tinnitus effect on life.

Introduction

At the London Tinnitus and Hyperacusis Centre patients with tinnitus and hyperacusis form the majority of our referrals. However a full spectrum of neuro-otological and otological conditions are encountered and treated. Over 95% of tinnitus and hyperacusis patients enter into a Tinnitus Retraining Therapy (TRT) programme, and all patients are offered this option. This is an habituation based treatment using the Jastreboff neurophysiological model where they are treated by a multi disciplinary team. The centre deals with many tertiary referrals, where treatment has been unsuccessful elsewhere.

This is an observational study carried out by the team and has not been subjected to randomisation and is not of a rigorous experimental design. It has been undertaken to give a realistic idea of the expectation and outcome of TRT in a clinic setting.

Method

Data has been taken from those patients seen between 1997 and 1999. All patients were seen by an otologist (mostly the second author) and were referred to the audiologist (first author) for management by TRT. Some patients were in a second term of treatment. TRT was carried out according to its strict criteria [1,2].

After audiometric evaluation and careful history taking [2] patients were allocated to Jastreboff diagnostic categories and treatment decisions made in accordance with this regime:

Category 1 with tinnitus, and no significant hearing difficulties;

Category 2 with tinnitus, and significant subjective hearing difficulties;

Category 3 hyperacusis with or without tinnitus, hearing loss irrelevant, and having no kindling effect as in Category 4;

Category 4 hyperacusis with or without tinnitus and with a prolonged effect on symptoms after noise exposure (kindling);

Category 0 tinnitus presenting as a minor problem, prolonged treatment not indicated.

Treatment decisions for:

Category 1 directive counselling and sound enrichment often using noise generators;

Category 2 counselling and sound enrichment with hearing aids to amplify environmental sound;

Category 3 counselling and desensitisation using noise generators;

Category 4 intensive counselling, sound enrichment with or without noise generators;

Category 0 one or two sessions of directive counselling with advice on sound enrichment.

For the purpose of this study the measurements used were:

- (1) Percentage awareness of tinnitus over the previous week during waking hours;
- (2) Percentage of the time it causes distress or annoyance;
- (3) Number of life factors affected (including concentration, quiet recreational activities, sleep, work, social, sport or family activities).

Data were recorded during a direct, structured interview with the patient, as we have found this to be more accurate than questionnaire data, although this can sometimes bias the answers.

Results

These are presented in three data sets. The first data set is from the first visit, and the second data set

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between six to twelve months after the first visit. The third and final data set was taken at the completion of treatment, or at the last clinic visit for those still in treatment. Some patients required to be seen more frequently than every six months, others delayed their second visit, so the second data set is taken from the visit closest to six months after the first visit.

The length of time between first and last visit is shown in Figure 1. The median time was 20.7 months (mean 27.7 months), but some patients remained in treatment for up to 93 months, mainly those patients in a second term of treatment, or those in category 2 (hearing aid group), who continue to attend for auditory habilitation and care of hearing aids. Figure 2 shows the number of patients reaching each data set. 483 patients were treated and entered into the trial without any selection process. The reduction of number of patients seen after the first visit is explained by some category 0 patients needing only one visit 4.8% ($n = 23$), those who have been in treatment for less than 6 months 4.8% ($n = 23$), and 12.4% ($n = 56$) who did not attend their next appointment (defaulters). Of the 381 patients reaching the second data set, there was a further reduction in numbers of which 6.8% ($n = 26$) were category 0, 16% ($n = 61$) were still in treatment less than 12 months and 18% ($n = 70$) were defaulters. The defaulters ($n = 126$) are excluded from the treatment outcome analysis, as they had not completed a proscribed course of TRT. The reasons for defaulting are discussed below

The age and sex distribution is shown in Figure 3. The age distribution is in agreement with other studies, however there was a preponderance of (young) males. The numbers of patients in each of the 5 diagnostic categories is shown in Figure 4. Only 4% fall into category 4, a smaller number than in studies published elsewhere. Table 1 shows the instruments that were fitted in each diagnostic category. Category 0 by definition received no instruments. Although we advocate binaural fitting of both wide band noise generators (WNG) and hearing aids, some patients were fitted monaurally, because of asymmetrical hearing loss, and occasionally because of lack of compliance. Instruments were fitted on open moulds wherever possible.

Evaluation of success of treatment follows a technique first devised by Jastreboff [3]. Using the '40% rule' (our practice) patients are assessed as being successfully treated, if they have either

- 40% improvement in annoyance and awareness; or
- 40% improvement in annoyance or awareness, plus an improvement/facilitation of one life factor.

The results of TRT are summarised in Figure 5. They show those patients who have achieved the 40% significance level of improvement (the better group) and those who have not (the no-better group). At six months 70% of patients have reached

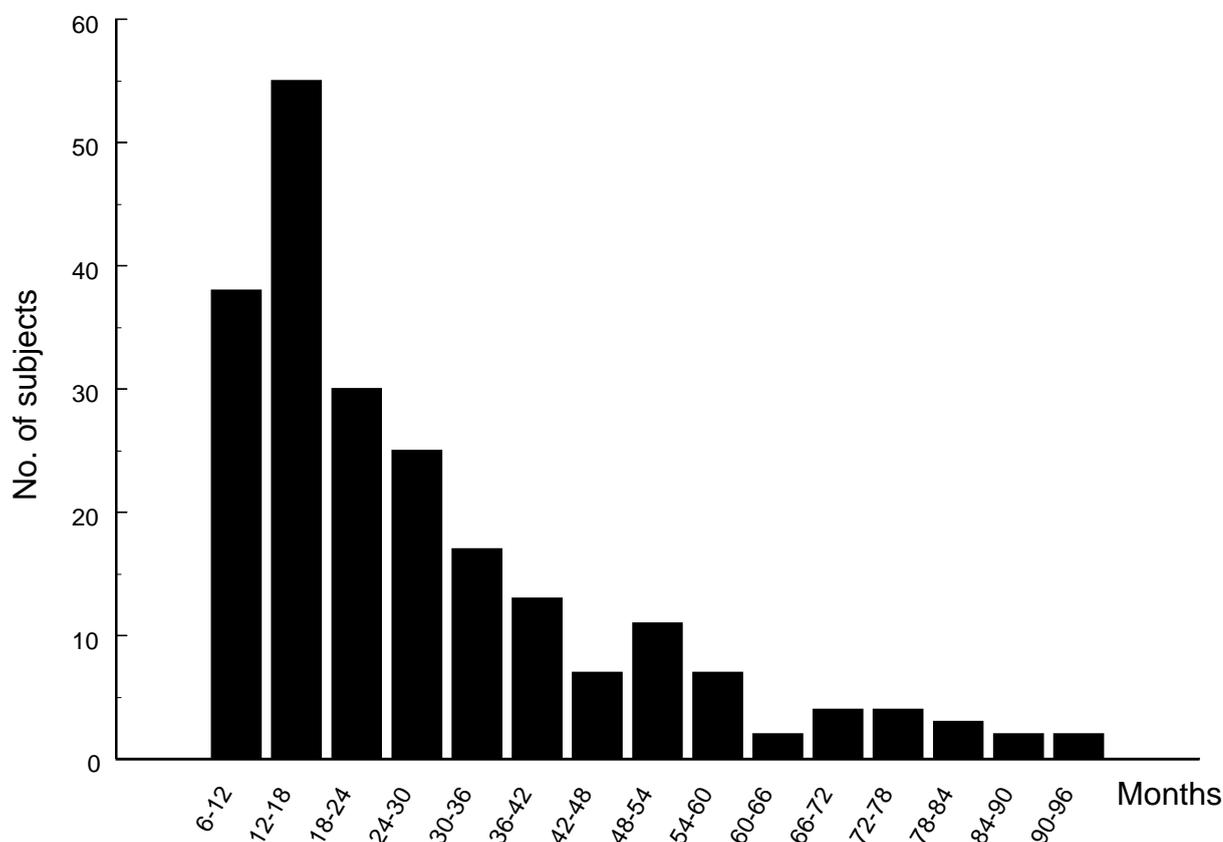


Figure 1 Time from first to last visit by numbers of patients

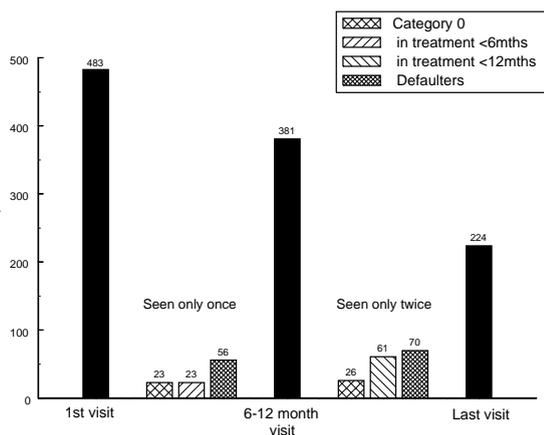


Figure 2 Number of patients in treatment at each data set

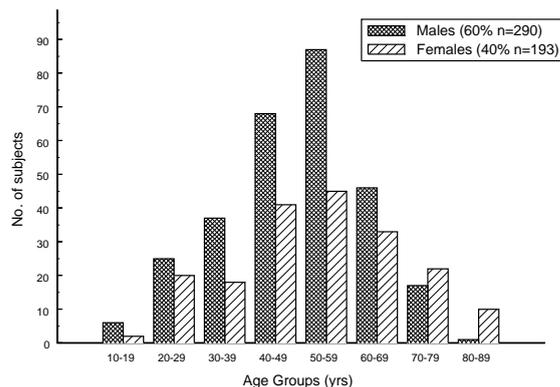


Figure 3 Distribution of patients by age and sex

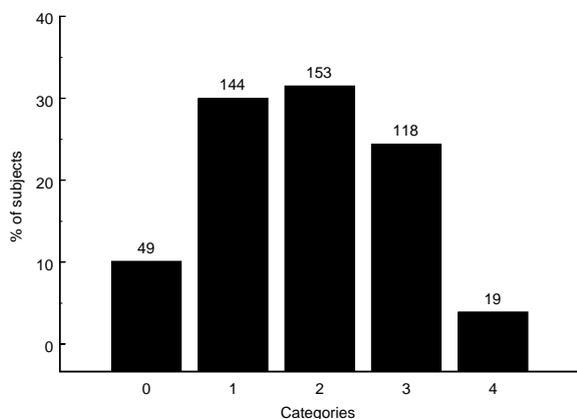


Figure 4 Distribution of patients by diagnostic category

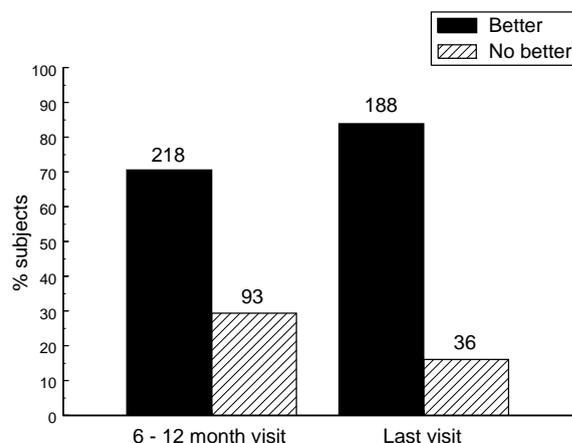


Figure 5 Percentage of patients achieving significant improvement. Defaulters are excluded from this analysis

Table 1 The instruments fitted within different categories. WNG wide band noise generators; HA hearing aids; Combi combination hearing aid and WNG; PA post aural; AIE all-in-the-ear; DC deep canal.

| Instrument | Category | | | | |
|------------|----------|-------------|----------------------------------|------------------------------|------------|
| | 0 | 1 | 2 | 3 | 4 |
| None | 49 | 26 | 23 | 23 | 2 |
| 1 WNG | 0 | 8 (PA) | 4 (2PA 2AIE) | 6 (PA) | 2 (PA) |
| 2 WNGs | 0 | 109 (PA) | 11 (PA) | 75 (PA) | 11 (PA) |
| 1 HA | 0 | 0 | 31 (8 PA 10 DC 13 AIE) | 6 (1 PA 5 DC) | 2 (AIE) |
| 2 HAs | 0 | 0 | 84 (51 PA 20 DC 13 AIE) | 8 (5 PA 2 DC 1 AIE) | 2 (PA) |
| Combi | 0 | | 1 (PA) | | |

this level of improvement, and by the last visit 83%. If the defaulters are included in the calculation the results at six months are unchanged (70.6% better).

The no-better group does not represent failure, only those patients not achieving 40% improvement by the time stated. The second data set at 6–12 months excludes the defaulters identified in Figure 2 (126 patients).

An analysis of the different components of habituation are shown in Figure 6. Mean awareness of tinnitus (indicating habituation of perception), and distress (indicating aversive reaction) are shown for 1st visit, 6–12 month visit, and last visit. Error bars indicate the standard error of the mean. In the ‘better group’, significant improvement in both habituation of perception and reaction are shown. This is clearly shown between the 1st and 2nd data set, and also between the 2nd and 3rd data set. In the ‘no-better’ group there was no significant improvement in distress or awareness over this time period. However a reduction in life factors affected by tinnitus did occur.

Discussion

This study shows that after treatment with TRT 83.9% of our patients from an unselected group of tinnitus referrals achieved a successful outcome on

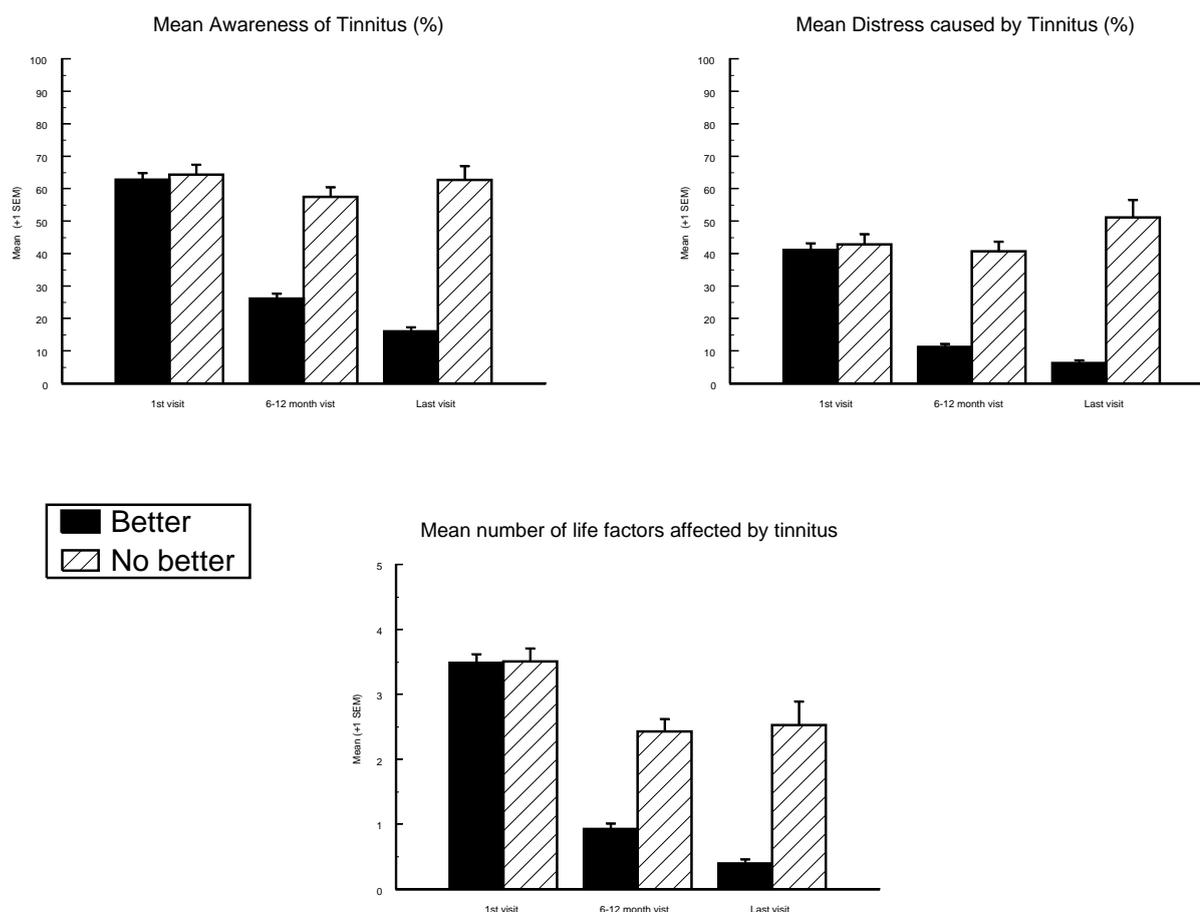


Figure 6 Mean levels of tinnitus awareness, distress and changes in life factors during treatment in the better and no-better groups

completing treatment. The criteria for success is strict and is chosen to help avoid any possibility of placebo effect. The success rate is also far above the highest estimated placebo effect for tinnitus treatment [4] and has been maintained over a 2-year period. Subsequent studies on this cohort of patients will look to see how this improvement is maintained over a longer period.

The process of habituation induced by TRT depends on plasticity, and plastic changes occurring in the central auditory system and its connections with the limbic and autonomic nervous system [5]. This process is a gradual one, particularly when it involves the reversal of powerful aversive conditioned reflex responses to tinnitus. This is clearly seen in Figure 6 in the group achieving significant improvement.

An important question is what happens to patients in the no-better group. Although they do not reach the level of significant improvement in the given time, this does not mean that they have not received any benefit from TRT. In Figure 6 it is clear that there is an improvement in life factors affected by tinnitus, even though awareness and dis-

trass from tinnitus is unchanged. From Figure 1 it is clear that some patients take considerably longer than the median 21 months to achieve habituation. It will be important to follow patients in the no-better group, who opt to continue in treatment, to see whether they do eventually reach significant levels of habituation or not.

In this study 126 (26%) of the initial patient group did not reach the final appointment. This is a high figure, and in the worst case could be seen as the percentage of patients who could not be helped by TRT. No calculations could be made for 56 patients who defaulted before the second visit, as data does not exist for them. However analysis of results for the defaulters at the 2nd data set (n = 70) showed that many of them had already achieved significant improvement. 52 defaulters (74.3%) had reached the criteria for the 'better group' by 6 months even though they had not completed full TRT. This suggests that after 6 months the majority of patients who do not keep their follow-up appointment do so because they do not feel the need for further treatment.

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Shifts in dynamic range for hyperacusis patients receiving tinnitus retraining therapy (TRT)

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A basic function of the initial evaluation for Tinnitus Retraining Therapy (TRT) is to assess and separate the four issues of tinnitus, hearing, hyperacusis, and phonophobia. Hyperacusis is defined as an abnormally strong response within the auditory pathways resulting from exposure to moderate sound. Phonophobia is the emotional or learned response to sound, and includes the fear of being exposed to certain sounds. The determination of the presence of hyperacusis and/or phonophobia entails the use of both a careful interview and the measurement of loudness discomfort levels (LDLs) during the initial evaluation. About 40% of the patients evaluated at the University of Maryland Tinnitus & Hyperacusis Center exhibit some degree of hyperacusis and enter into a carefully prescribed variant of the TRT protocol. This part of the protocol begins with directive counseling to review the test results with the patient and ensure that the patient clearly understands both the concepts of tinnitus and hyperacusis and the goals of the treatment plan. Patients are also instructed in the appropriate use of noise protection, the detrimental use of overprotection, and the use of low-level, broad-band noise generators (NG).

To monitor change or lack of change in tolerance levels during treatment, pure tone thresholds, loudness discomfort levels (LDLs), and patient interviews are repeated as part of each follow-up evaluation. Data will be presented for change in dynamic range (DR) of patients with initially reduced tolerance levels. Initial measurements of pure tone thresholds and LDLs for 1, 2, and 4 kHz will be compared with measurements at follow-up evaluations for patients who received directive counseling and were fit with low-level, broad-band noise generators (NG) as part of the TRT hyperacusis protocol. Results for 130 adult ears (72 male ears, 58 female ears), which met the aforementioned criteria, indicate a statistically significant improvement in LDLs at each test frequency, while audiometric thresholds remained stable. These results will be discussed and related to the associated subjective improvement in the quality of life of hyperacusis patients.

Introduction

For the past decade, patients suffering from tinnitus have been treated at the University of Maryland Tinnitus & Hyperacusis Center using a clinical protocol based on a neurophysiological model of tinnitus [1]. This protocol involves the use of directive counseling and external low-level sound to induce and facilitate both habituation of the reaction to and habituation of the perception of the tinnitus signal [2]. Much of the refinement of the clinical protocol, which is now called Tinnitus Retraining Therapy (TRT), has taken place in our center. The TRT protocol, in modified form, has also been used successfully to treat hyperacusis and phonophobia.

Hyperacusis is defined as an abnormally strong

response within the auditory pathways resulting from the exposure to moderate, or even soft, sound levels. It is manifested, clinically, by reduced loudness discomfort levels (LDLs), and is frequently reported as physical discomfort and/or feelings of pressure or fullness in the ear. Phonophobia is the emotional or learned response to sound, with strong reaction of the autonomic and limbic systems. It may include the fear that certain sounds will exacerbate tinnitus and/or cause hearing loss, but it usually does not involve physical discomfort or reduced LDLs. Overall increased sound sensitivity is generally the result of a combination of both hyperacusis and phonophobia. Interview questions and directive counseling currently used in TRT attempt to separate these phenomenological issues for both the clinician and the patient.

From an historical perspective, when the clinical program was first established at the University of

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Maryland in 1990, the main emphasis was on tinnitus. Questions about tolerance problems during the initial patient interview were not as detailed as they are now, and the impact of phonophobia had not yet evolved as an important factor. Measurement of LDLs for both live voice and pure tones, however, were always included in the initial tinnitus evaluation and in follow-up testing as part of the complete battery [3]. As patients underwent treatment in our center, we began to see improvements in their LDL measures. If a patient had normal LDLs initially, and those levels shifted to even higher LDLs, then it was speculated that those shifts might indicate a reduction in the "gain" of the auditory system [2]. Because there was no initial complaint in the area of tolerance problems or sound sensitivity, no subjective improvement was usually noted by these patients. If, however, initial LDLs were reduced (i.e. <100 dB HL), and subsequently improved at follow-up testing, those patients generally reported a significant improvement in their tolerance to sound and in the quality of their lives. They were better able to perform activities that were previously too uncomfortable to tolerate, such as riding in a car, going to shopping malls, supermarkets, and work, attending church services, hearing dishes clatter, and being around young children. Improvements in the area of tolerance to sound tended to occur more quickly than changes in habituation of the tinnitus signal. For some of these patients, as tolerance levels improved, tinnitus also became less of an issue. For others, tinnitus remained a significant problem. In either case, treatment continued toward the goals of habituation and making tinnitus a "non issue" in the patient's life.

As these patterns emerged, we began to evaluate and treat patients with reduced tolerance levels in a more specific way, developing a variant of the basic tinnitus protocol. Treatment categories specifically related to hyperacusis were developed, and directive counseling was expanded to include the issues of hyperacusis, and, subsequently, phonophobia. As a consequence, in the current TRT protocol, if hyperacusis is present, then it is always addressed and managed before the tinnitus [2]. In our center, approximately 40% of the tinnitus patients exhibit some degree of reduced tolerance to sound.

This study quantifies functional auditory changes (demonstrated by increases in LDLs and dynamic range (DR) at the audiometric frequencies 1, 2, and 4 kHz) during TRT for tinnitus patients who also experienced varying degrees of hyperacusis. In this study, we derive the DR from the dB difference between the LDL and the audiometric pure tone thresholds at a given frequency. We will present evidence that increases in the DR are directly related to improvements in LDLs, and are not due to improved hearing thresholds.

Methods

Subjects

Patients with clinically significant hyperacusis were selected from the University of Maryland Tinnitus & Hyperacusis Center database. The primary selection criterion for hyperacusis was average LDLs in both ears for 1, 2, 4 and 8 kHz below 100 dB HL [4], in addition to patient reports, during the initial interview, of physical discomfort when exposed to certain sounds. Our sample consisted of 130 adult ears with hyperacusis (72 male ears, 58 female ears). No subject was diagnosed with Meniere's Syndrome or had a history of fluctuating hearing loss. All patients had received directive counseling to review the test results and ensure that they clearly understood, both the concepts of tinnitus and hyperacusis, and the goals of the treatment plan [5]. They were fitted with binaural, broad-band noise generators (NG), and received instruction in their use. According to the hyperacusis protocol for TRT [6], patients were trained to set the volume of the NGs, initially, slightly above their threshold of hearing. After several weeks of using the NGs, we discussed progress with each patient. At that time, they were typically instructed by the clinician to increase the NG volume slightly more to attain a perceived "mixing point" (the sound of the NG blends with the tinnitus), where the volume setting generally remained for the duration of the treatment. The sound of the NG never masked the tinnitus.

Instrumentation

A diagnostic audiometer (GSI, model 1710) was used for initial and follow-up measurement of audiometric thresholds in the frequency range from 0.25 Hz to 12 kHz, and for measuring LDLs at 1, 2, 4, 8 and 12 kHz. Test stimuli were presented using earphones (Telephonics, model TDH-50P) encased in MX-41/AR cushions. The responses were recorded within a computerized database (Audiologic Software, version 5.6).

The low-level, broad-band NGs were selected because they offered a well controlled, stable source of sound. NGs were either behind the ear devices (Viennatone, models AMTi, ARPPTi, or Silent Star) with non-occluding earmolds (Microsonic Laboratories, #19 Free Field), or non-occluding, in the ear units (General Hearing Instruments, model Tranquil). Patients chose whichever style they preferred, and were fitted binaurally.

Functional test procedures

Subjects were seated in a sound attenuating, single-walled sound booth (IAC, model 403). The audiologist controlled the audiometer from outside the test booth. Audiometric thresholds were obtained using the conventional Hughson-Westlake procedure [7]. LDLs were obtained by instructing the patient to press a response button "when the sound gets to the point where it would be too loud to tolerate for very long; try to hold off as long as

possible". LDLs were measured with brief pure tone stimuli presented in ascending 5 dB steps, with randomized starting points. Due to the potential for physical discomfort and the need for our patients to feel a sense of control during the testing, we did not use a completely randomized presentation pattern (which has been recommended to reduce sequential bias [8]). The LDL procedure was repeated twice for each ear, and the second response was recorded. Measurements for 8 and 12 kHz were available, but will not be included in this analysis due to limitations in the output levels of the audiometer at those frequencies. The patient's hearing thresholds and LDLs were assessed at both initial and TRT follow-up evaluations using the same procedures. Average time between the initial tests and the follow-up tests was 8.97 months (*s.d.* = 4.76).

To quantify changes in auditory function during TRT, we performed a retrospective analysis of the (1) audiometric thresholds, (2) LDLs, and (3) DR at 1, 2 and 4 kHz for each ear in our sample. Values from the initial evaluation were compared to those same measures from the follow-up evaluation. In addition, subjective assessment of change was examined for 48 of the patients. This assessment was based on answers to initial and follow-up interview questions that were directed at establishing the effect of hyperacusis on the patient's quality of life and daily activities. Specifically, we sought to quantify those daily activities initially prevented or affected by hyperacusis and the perceived improvement at the follow-up interview.

Results

The functional changes between initial and follow-up evaluations are summarized in Table I for the audiometric thresholds, LDLs, and DR. Results are presented separately for 1, 2 and 4 kHz, and for the overall change averaged across the three frequencies.

Audiometric Thresholds

No significant changes occurred between the initial and follow-up hearing threshold measures. The mean hearing threshold change was 1.60 dB at 1 kHz, 1.85 dB at 2 kHz, and 0.04 dB at 4 kHz. The

overall mean threshold change between initial and follow-up tests revealed only slightly diminished detection (1.16 dB) at follow-up, which is well within the range of test-retest reliability.

Loudness Discomfort Levels (LDLs)

In contrast, significant changes were noted in LDL measurements over time. Mean LDL changes were 12.52 dB at 1 kHz, 12.72 dB at 2 kHz, and 12.20 dB at 4 kHz, with an overall mean change across these three frequencies of 12.48 dB. The mean LDLs at follow-up testing were at or near normal LDL thresholds (100 dB HL) for each frequency. Mean LDL at follow-up testing was 101.22 dB HL at 1 kHz, 99.27 dB HL at 2 kHz, and 101.50 dB HL at 4 kHz.

Dynamic Range (DR)

Significant increases in DR between the initial evaluation and follow-up tests were seen at all test frequencies. The mean increase in DR at individual frequencies between initial evaluation and follow-up was 10.92 dB at 1 kHz, 10.87 dB at 2 kHz, 12.16 dB at 4 kHz. The overall mean change for these frequencies was 11.32 dB.

Assessment of Subjective Change

During initial and follow-up interviews, each patient was asked to rate the combined effect on quality of life of tinnitus, tolerance problems, and hearing loss, if present. The rating scale used an ordinal range between zero (no effect) and 10 (life is totally ruined). Ratings from 48 of the patients selected for this study revealed that the mean effect on quality of life was 7.38 (*s.d.* = 2.60) at initial interview, and was reduced to 4.13 (*s.d.* = 2.64) at the follow-up interview.

A second outcome measure analyzed the number of activities that the patient was prevented from doing or was interfered with by tolerance problems. Activities reported at the initial evaluation were compared with answers at the follow-up interview for the same 48 patients above. The mean number of activities at the initial interview was 4.80 (*s.d.* = 3.08), and the mean number at follow-up was 1.38 (*s.d.* = 2.06). This change reflects a substantial

Table 1 Changes between initial and follow-up evaluations for audiometric threshold, loudness discomfort level, and dynamic range for 1, 2 and 4 kHz, and overall. Results are shown as mean (and *s.d.*) change in dB.

| Frequency (Hz) | 1k | 2k | 4k | Overall |
|---------------------------|--------------------|--------------------|--------------------|--------------------|
| Audiometric Threshold | 1.60 (5.22) | 1.85 (9.08) | 0.04 (5.99) | 1.16 (7.00) |
| Loudness Discomfort Level | 12.52** (11.83) | 12.72** (14.93) | 12.20** (14.05) | 12.48** (13.63) |
| Dynamic Range | 10.92** (12.20) | 10.87** (16.5) | 12.16** (14.20) | 11.32** (12.19) |

*Highly significant ($p < 0.0001$)

increase, on average, in the number of activities that each patient was able to participate in comfortably consequent to TRT.

Discussion and conclusions

The results of this study show that DR can be increased for hyperacusis patients using low-level, broad-band sound in a carefully prescribed protocol with directive counseling. The sizeable and statistically significant increases in DR are due to supra-threshold changes. These changes reflect significant improvements in LDL, and are not due to improved hearing thresholds, which remained stable between initial and follow-up evaluations. These changes also seem to be related to subjective improvement in the quality of life among our hyperacusis patients. Comparisons of ratings based on effect on life (0 to 10) may be viewed as a subjective indication of overall functional improvement for tinnitus, hyperacusis, and hearing loss (if present) combined. It does not reflect the changes based on hyperacusis alone. Questions and ratings for both initial and follow-up interviews are currently being revised in our center to address the issue of hyperacusis more specifically. Interview questions related to the number of activities prevented by or affected by tolerance problems are currently specific to hyperacusis.

Average time between initial and follow-up testing for this study was 8.97 months. This length of time is influenced by the large proportion of our patients who had to travel long distances for their appointments. Future investigation will attempt to decrease the length of time between test-retest to assess more accurately the rate at which LDLs and DR improves. Clinical observations in our center have revealed individual increases in DR of 15 dB to 45 dB within an 8-week period. Hazell and Sheldrake have reported smaller, stable LDL shifts over the same time course [9]. Investigation is ongoing to determine if DR continues to increase over a longer period of time, and if that increase remains stable. Preliminary data indicates that it does. Ultimately, the amount and rate of DR change can be expected to depend on how much change is necessary to reach the normal LDL range. It is reasonable to expect that DR change to normal limits will depend on the initial LDL values, and LDLs that are very reduced may be anticipated to take longer to reach normal levels.

It is interesting to note that hearing thresholds remained stable for our patients over the ongoing course of TRT. This is an expected, but nonetheless important, result because it demonstrates that chronic use of low-level, broad-band NGs for a minimum of 8 hours per day for an average of 8.97 months was not audiometrically harmful.

That appreciable LDL and DR changes do occur among hyperacusis patients receiving appropriate management has clinical implications. For too long, patients with complaints in this area have been dismissed by well-meaning professionals who have not

known how to evaluate or treat this population. Indeed, many patients who complain about tolerance problems have been, incorrectly, advised to "go home and wear earplugs", which is exactly the opposite of what they should be doing. There is, of course, a role for appropriate ear protection from loud noise. Overprotection (against low or moderate level noise or "just in case"), however, can be just as detrimental as underprotection and can exacerbate both tinnitus and hyperacusis. According to the neurophysiological model upon which TRT is based, when the brain receives attenuated sound (overprotection), it turns up the "gain" of the auditory system. This may result in increased supra-threshold sensitivity [2]. The tolerance problems generally get worse, and the patients enter into a cycle of increased isolation and anxious attempts to control their sound environment. This often has detrimental effects on family, work, and social activities. Our patients and their families are, therefore, carefully counseled about the role of appropriate ear protection and the importance of sound exposure in their environment.

Audiologists and otolaryngologists should be aware that reduced DR (due to reduced LDLs) may be present in patients with normal/near normal audiometric thresholds as well as in patients with hearing loss. Evidence has been presented that reduced LDLs can often be shifted with the use of directive counseling and low-level, broad-band sound therapy. In many cases, patients with significant hearing loss and reduced DR are not considered candidates for amplification, or if they try hearing aids, these trials are frequently unsuccessful. Often, no treatment is offered for the tolerance problems and LDLs may not even be retested, under the assumption that they never change. Our experience has been that, if this low-tolerance population is treated for hyperacusis first, then they are generally able to make a comfortable transition to appropriate amplification within about 8 months to 1 year. This observation is potentially very important, clinically, because the existing literature is not convincing that tolerance training using high-level sound is successful for improving LDLs [10]. The use of low-level sound therapy, however, does appear to be effective in achieving enhanced tolerance.

In summary, TRT offers a comprehensive approach to evaluating and treating hyperacusis patients. With the use of low-level, broad-band noise generators, directive counseling, careful interview, and follow-up, many hyperacusis patients can and will successfully achieve the goal of living comfortably in a busy, noisy world.

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Controlled prospective study of tinnitus retraining therapy compared to tinnitus coping therapy and broad-band noise generator therapy

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In a controlled study we investigated the efficacy of pure broad-band Noise Generator Therapy (NGT) in comparison to Tinnitus Retraining Therapy (TRT) and pure behavioural Tinnitus-Coping Therapy (TCT). In the first part of our study, 52 patients with chronic decompensated tinnitus and unimpaired hearing were randomly assigned one type of outpatient treatment while waiting for placement in our clinic: (1) The NGT group were fitted with noise generators (Silent Star-Viennatone™). A brief counselling by telephone regarding the theory and use of NG was included. (2) The TRT group participated in outpatient group tinnitus coping therapy (groups of about 8 patients, 4 Saturdays during 4 months). Additionally, they were fitted with NG. (3) The TCT group received the same treatment as the TRT group, only without NG therapy. (4) The patients in the control group (waiting-list WLG) received no therapy.

At the end of a six to eight weeks inpatient therapy we randomly selected 51 other patients with the same inclusion criteria and randomly assigned them to different types of ongoing outpatient treatment. (5) In the "Post-NGT-group," patients were fitted with NG when leaving the clinic (NGT-post), or (6) participated in booster sessions similar to TCT (TCT-post). (7) The "TCT-refusal-group" consisted of patients who did not want to join in the "Post-TCT-group" and therefore received no further treatment. (8) The "Post-Control-group" received no specific therapy (Control-post).

The treatments were evaluated using the Tinnitus Questionnaire (TQ), Visual Analogue Scales (VAS) reflecting tinnitus annoyance, tinnitus control and hyperacusis, the Beck Depression Inventory (BDI) and Symptom-Check-List (SCL-90-R) regarding general symptoms.

Results: Due to the restrictive selection of patients, both studies are still in progress, so the results presented here are preliminary. The psychiatric comorbidity of all participating patients was high (DSM-IV; SCL-90-R). While the participants who have already completed the TRT or the TCT displayed clinically relevant improvements regarding tinnitus annoyance (TQ; $p = <0.05$), tinnitus control ($p = <0.05$), and depressiveness (BDI $p = <0.05$), the results in the NGT-group are unsatisfactory. There were no differences between the groups regarding tinnitus control or hyperacusis in the pre-admission period.

The post-discharge interventions showed no specific effect on the course of tinnitus annoyance.

Preliminary conclusions: For patients with decompensated tinnitus, the effect of NGT is advantageous only with a strong focus on counselling with cognitive interventions. Intensive cognitive-behavioural oriented coping treatments which by far surpass the requirements stated by Jastreboff and Hazell [1], supported by technical aids (TRT), is equally effective after four months to behavioural coping treatment (TCT).

Introduction

Recently, Tinnitus Retraining Therapy (TRT) as conceived by Jastreboff [1,2] has received an increasing amount of attention in the general as well

as scientific media on treatment methods for chronic tinnitus. Jastreboff's theoretical conception of tinnitus as a neurophysiological disorder has been evaluated and found to be supported by some evidence. The interaction between neuroacoustical and emotional processes is, however, neither new nor has it been sufficiently elaborated in regard to the underlying psychological factors. The TRT interventions with its main components 'directive

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counselling' and the use of 'noise generators' are theoretically grounded. According to Jastreboff, TRT does not encompass psychotherapy [3], however, the TRT therapist should be very experienced in counselling and should have as much experience with tinnitus patients as possible. The lack of controlled randomised group studies and the potential consequence that differing interventions are offered under the name of TRT poses a scientific problem and is criticised [4,5,6,7]. By contrast, there is more substantial empirical support for the efficacy of cognitive-behavioural interventions in reducing tinnitus annoyance and tinnitus-related suffering. The necessity of methodologically well-designed studies to determine effectiveness of TRT and compare it with other techniques, especially cognitive-behavioural (TCT) is evident. In addition, it is of interest whether the effects of TRT can be traced back mainly to partial tinnitus masking or to the intensive counselling part of treatment. The study presented here is designed to meet these demands.

Methods

Design

The experimental conditions were: pure broadband Noise Generator Therapy (NGT), Tinnitus-Retraining Therapy (TRT), Tinnitus Coping Therapy (TCT) and a waiting-list control (WLC). Patients who refused to participate in post-dismissal TCT were re-examined in a follow-up study (control-post). The design is summarised in Table 1.

Subject selection

From patients with chronic decompensated tinnitus (global score 40 to 70 points on the German Tinnitus Questionnaire TQ) referred consecutively for inpatient behavioural psychotherapy, a sample of 52 with unimpaired hearing (hearing threshold <30 dB) [8] were chosen and randomly assigned to different groups. Since the aim of the study was to evaluate the efficacy of interventions in stable decompensated chronic tinnitus [9], patients with Menière's disease, acoustic neurinoma, otosclerosis, severe general health problems, and psychoses were excluded. We also excluded patients previously treated with noise generators resp. maskers. Most exclusions were pronounced due to disturbances of auditory function. Patients with a TQ-global score >70 were excluded for ethical reasons. These patients were admitted as quickly as possible. All patients were thoroughly checked for neurological and otological disease, and psychoacoustic parameters (intensity, minimal masking level MML, loudness discomfort level LDL, etc.) were documented. During the course of the study, the patients received no medication relevant for tinnitus.

Measures and assessment sequence

The TQ [9,10] was used to assess the dependent variable "tinnitus severity". It is one of the most

sensitive instruments and scores highly in validity and reliability [11]. Its global score (range 0–84) correlates with the visual analogue scales (VAS) tinnitus annoyance" and volume around $r = 0.75$ [10]. Additionally, the variables "tinnitus annoyance", "tinnitus control", "hyperacusis", NG protocol, Hopkin's Symptom Check-List (SCL-90-R; [12]) and Beck's Depression Inventory (BDI; [13]) were collected. We evaluated psychiatric co-morbidity according to DSM-IV. Measurement times were application for inpatient therapy resp. beginning of the pre-admittance outpatient therapy (T0), the end of the pre-admittance outpatient treatment resp. admittance (T1); discharge (T2); end of the post-discharge outpatient treatment, resp. 6-month follow-up (T3). The total observation period was up to 14 months.

Treatment procedures

The TCT and TRT groups consisted of 7 to 10 participants each. Altogether, there were 4 Saturday sessions of four-and-a-half hours each, given in the Klinik Roseneck. On the basis of behavioural therapy, the participants received detailed counselling concerning tinnitus causes and maintenance, methods of tinnitus and stress coping, interventions towards changes in attitudes, and exercises in attention focusing. Patients in the TRT group were also fitted with a broad-band noise generator (Silent Star-Viennatone™) with an open auricle-piece, and were given detailed instructions as to its use and effects. The neurophysiological tinnitus model [1,2] is part of the therapeutic concept.

Patients in the NGT group received the same noise generator (Silent Star-Viennatone™) and were given instructions by mail or by telephone about its use. In the control groups (WLC, Control-post), no therapy was offered.

Psychiatric Co-morbidity

Since we included only patients with a medium-to-high severity score in the TQ, nearly all groups displayed comparably high rates of psychiatric co-morbidity (Table 1). The extent of current overall complaints can be gauged by the high "Global Symptom Index" (GSI) of the Hopkin's-Symptom-Check-List SCL-90-R [12].

Sociodemographic data

The samples consisted of altogether 65 males and 38 females. The tinnitus history encompassed an average of 35 months (± 40 months; range 0.6 to 11 years). The groups displayed comparable psychosocial statistics: mean age 44 ± 13 years; range 27 to 62 years; married: 70%, divorced: 10%, unmarried: 10%, university-qualifying education: 30 to 40%, employed: 70%, retired: 20%.

Statistics

The data were analysed using the statistics software SPSS 4.0. First, a multivariate variance analysis

Table 1 Psychiatric Co-morbidity (prevalence, multiple diagnoses according to Diagnostic and Statistical Manual of Mental Disorders DSM-IV of the American Psychiatric Association) in patients with chronic decompensated tinnitus [TQ global score ≥ 40 – ≤ 70 ; [11]. GSI = “Global Symptom – Index” of the Hopkin’s-Symptom-Check-List SCL-90-R [12].

| DSM- IV- diagnosis: | NGT-pre n = 16 | TRT-pre n = 10 | TCT-pre n = 7 | WLC n = 19 | NGT-post n = 5 | TCT-post n = 15 | refusers n = 12 |
|------------------------------------|-------------------|-------------------|------------------|---------------|-------------------|--------------------|--------------------|
| no disorder | 27% | 15% | 14% | 16% | 0% | 5% | 18% |
| Major Depression | 64% | 60% | 43% | 36% | 84% | 77% | 48% |
| Dysthymia | 10% | 6% | 14% | 32% | 21% | 22% | 27% |
| Anxiety disorder | 55% | 30% | 56% | 26% | 51% | 49% | 29% |
| Somatoform disorder | 36% | 28% | 27% | 20% | 37% | 22% | 19% |
| SCL-90-R: GSI; abnormal >0.62 | 1.0 ± 0.5 | 0.9 ± 0.4 | 1.1 ± 0.5 | 1.0 ± 0.6 | 0.9 ± 0.4 | 0.8 ± 0.5 | 0.9 ± 0.6 |

(MANOVA) was performed to discover time or interactional effects between the groups. With T-tests for dependent samples, we examined in which groups significant changes between measurement times could be found.

Results

A summary of the means and standard deviations for each dependent variable at pre-treatment, post-treatment and follow-up assessments is provided in Table 1.

Attention to the mean values may result in some concern over possible differences between groups: Similarly to the WLC, the NGT-pre group had the highest annoyance value at both measurement times ($F = 8.1$; $p = <0.01$), the highest value for hyperacusis (70 ± 23 ; $F = 3.2$; n.s., not listed in the tables) and the highest TQ-Score ($F = 4.7$; $p = <0.05$; Table 2). This cannot be explained by the psychiatric co-morbidity (Table 1), nor by depressive complaints (BDI). The TRT-pre- and TCT-pre-groups have similar primary scores except for the BDI, which was highest in the TCT-pre-group ($F = 6.1$; $p = <0.001$). In the post-study, the patients in the TCT group did not differ from the control group (Table 3).

Taking into account that the patients in the NGT-pre-group had a higher score to begin with, and that the examined time frame was four months, the “pre”-study reveals that the TRT and TCT groups have outcomes superior to NGT with regard to improvement of the variables annoyance“ ($F = 6.1$) and “tinnitus severity” as measured with the TQ ($F = 12.8$; $p = <0.01$; Table 2). The most profound effect of TCT was measured in the variable “control” ($p = <0.05$) and equal to TRT in the variable TQ ($F = 3.0$; $p = <0.05$). On the general symptom level (GSI in SCL-90-R), no significant differences were found between the groups, whereas depressiveness (BDI) declined more in the TRT group than in the other groups ($F = 3.9$; $p = <0.05$; Table 2). In four months, NGT was shown to be ineffective with regard to the measured variables. We plan to complete the study including examinations of how the patients from different study arms react to inpatient psychotherapy. The data collected so far are insufficient to permit conclusions at this point.

Table 2 Pre-study; Means and standard deviations (\pm); BDI = Beck Depression Inventory [13]; TQ = Global Score of the Tinnitus Questionnaire TQ [10]. Significant differences are marked with asterisks *; for sign. results of the variance analysis see section on results.

| groups | variables | first contact | admission |
|-----------|-----------|---------------|---------------|
| Pre-study | Annoyance | T0 | T1 |
| NGT-pre | n = 16 | 75 ± 20 | 70 ± 22 |
| TRT-pre | n = 10 | 53 ± 12 | 45 ± 18 |
| TCT-pre | n = 7 | 57 ± 25 | 42 ± 16 |
| WLC | n = 19 | 75 ± 21 | $60 \pm 25^*$ |
| | Control | T0 | T1 |
| NGT-pre | n = 16 | 36 ± 25 | 35 ± 26 |
| TRT-pre | n = 10 | 51 ± 16 | 55 ± 20 |
| TCT-pre | n = 7 | 39 ± 30 | $62 \pm 17^*$ |
| WLC | n = 19 | 28 ± 25 | 21 ± 24 |
| | TQ | T0 | T1 |
| NGT-pre | n = 16 | 56 ± 9 | 55 ± 13 |
| TRT-pre | n = 10 | 47 ± 9 | $39 \pm 12^*$ |
| TCT-pre | n = 7 | 51 ± 15 | $41 \pm 12^*$ |
| WLC | n = 19 | 54 ± 8 | 54 ± 8 |
| | BDI | T0 | T1 |
| NGT-pre | n = 16 | 17 ± 6 | 18 ± 8 |
| TRT-pre | n = 10 | 17 ± 7 | $12 \pm 6^*$ |
| TCT-pre | n = 7 | 23 ± 13 | $16 \pm 6^*$ |

In Table 3, pre-admission data has been included to illustrate the spontaneous course of tinnitus variables without (T0 vs. T1) and with multimodal inpatient therapy (T1 vs. T2). The inpatient treatment of 6 to 7 weeks (mean) was similarly effective in most of the post“ groups. This reflects data of earlier studies [11,14]. Only those patients who did not participate in the “booster session” of TCT at the end of inpatient treatment (TCT-refusals), were then the patients with the smallest therapeutic success.

In the “post”-study, neither TCT nor NGT had a significant effect on the further course of tinnitus variables. Over the course of the whole study (T0 vs. T3), TCT after discharge was not superior to control group results in the variable “tinnitus severity” (measured with TQ). NGT offered for 6 months after discharge was also ineffective as compared to controls. The effect of NGT on “hyperacusis”, measured with VAS (not listed in the tables), showed no advantage over other therapies, but due to the low mean score (30 ± 27), this does not seem particularly relevant. TCT had no significant effect

Table 3 Post-study: Significant differences are marked with asterisks* (T0/T1), ** (T1/T2); **** (T0/T3); the "post"-study deals with the differences between T2 and T3; for sign. results of the variance analysis see section on results

| groups | variables | first contact | admission | discharge | follow up |
|--------------|-----------|---------------|-----------|-----------|--------------|
| Post-study | Annoyance | T0 | T1 | T2 | T3 |
| NGT-post | n = 5 | 90 ± 6 | 84 ± 9 | 46 ± 19** | 42 ± 27 **** |
| TCT-post | n = 15 | 73 ± 16 | 59 ± 21* | 66 ± 13 | 65 ± 12 **** |
| TCT-refusals | n = 12 | 60 ± 19 | 74 ± 13 | 54 ± 11** | 54 ± 23 |
| Control-post | n = 18 | 68 ± 21 | 81 ± 15 | 56 ± 23** | 60 ± 21 |
| | Control | T0 | T1 | T2 | T3 |
| NGT-post | n = 5 | 18 ± 10 | 10 ± 12 | 54 ± 31** | 56 ± 23 **** |
| TCT-post | n = 15 | 41 ± 29 | 30 ± 20 | 43 ± 22** | 54 ± 17 **** |
| TCT-refusals | n = 10 | 44 ± 26 | 25 ± 18 | 55 ± 18** | 51 ± 27 |
| Control-post | n = 18 | 33 ± 27 | 34 ± 22 | 50 ± 27** | 62 ± 24 **** |
| | TQ | T0 | T1 | T2 | T3 |
| NGT-post | n = 5 | 52 ± 12 | 56 ± 10 | 39 ± 20** | 44 ± 9 **** |
| TCT-post | n = 15 | 55 ± 10 | 55 ± 10 | 49 ± 13** | 49 ± 9 **** |
| TCT-refusals | n = 13 | 52 ± 12 | 53 ± 7 | 50 ± 15** | 47 ± 22 **** |
| Control-post | n = 18 | 58 ± 11 | 59 ± 7 | 43 ± 18** | 47 ± 16 **** |
| | BDI | T0 | T1 | T2 | T3 |
| TCT-post | n = 15 | | | 17 ± 10 | 16 ± 9 |
| Control-post | n = 18 | | | 17 ± 8 | 13 ± 9 |

on depressive symptoms (BDI; Table 3) or other general symptoms (GSI; not listed in the tables). The patients who refused to participate in the TCT offered them, displayed no differences from other groups with regard to the pre-admission course (T0 – T2).

Discussion and conclusions

With our findings, the efficacy of TRT, modified in accordance with the German standard of treatment by qualified psychologists [7], is confirmed in a prospective, randomised and controlled study for the first time. This is shown especially by a score reduction in the TQ [10,11]. Thus, our study confirms the findings of Biesinger *et al.* [5], who treated a similarly affected sample without hearing impairment in an uncontrolled and individual outpatient study. Of interest is the high psychiatric comorbidity of our samples, which made it necessary to offer therapeutic support beyond Jastreboff's TRT-curricula. Other evaluations in a 4-week TRT cannot be compared with ours, since a patient group with low-grade impairment (exclusion of patients with a TQ score ≥ 40 points) was treated with lower levels of psychiatric co-morbidity. Compared with our results, the same researchers achieved even more pronounced effects with a group of similarly affected patients during a 10-week TCT [15].

A further result in our study is that TRT, conducted by a psychologist with experience in tinnitus, is just as effective as TCT. Moreover, both therapeutic options alleviate depressive symptoms (BDI). It is unclear why the therapies offered after discharge (TCT) were unable to further affect depressive symptoms.

The decisive element of TRT is counselling.

Thus, in our severely compromised patients treated with NGs alone, there is no effect on tinnitus-specific variables. Although certain patients did improve, others displayed a further deterioration of their condition. Even if the observation time of less than 6 months is taken into account, on the average, improvements should show. TCT offered after discharge does not improve tinnitus complaints.

Further studies in addition to the continuation of the research presented here will need to answer the question to what extent psychological treatment (TCT, TRT) or NGT before admission to a clinic is beneficial either to enhance subsequent inpatient behavioural-psychotherapeutic treatment or even to replace it.

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Perceptual changes in tinnitus subjects: Correlates of cortical reorganization?

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Results in the literature indicate that phantom limb pain is associated to neural reorganization in the somatosensory cortex following amputation. The present study was aimed at testing the hypothesis that tinnitus may be associated to increased tonotopic representation of a narrow frequency range in the auditory cortex due to focal hearing loss. In this purpose, advantage was taken of the possibility of investigating alterations in the neural tonotopic map in humans via differences in frequency-discrimination limens (FDLs) across frequencies. FDLs were measured at and around the estimated frequency of the tinnitus in 6 patients. The results so far reveal that FDLs are significantly decreased at the frequency of the tinnitus or at nearby frequencies than at other frequencies. Furthermore, comparisons between the left and right ears of patients suggest that the variation in FDLs across frequencies does not proceed simply from peripheral factors, i.e. changes in absolute thresholds across frequencies around the tinnitus frequency – but rather reflect central processes. This result agrees with the notion that tinnitus is associated to increased neural representation of certain frequencies in the auditory system.

Introduction

Cochlear lesions have been shown to induce reorganization in the representation of frequencies at the level of the auditory cortex. Specifically, it has been shown that following the lesion of a restricted portion of the cochlea, the receptive fields of cortical neurons which formerly responded to frequencies that are no longer stimulated are altered in such a way that these neurons start responding to neighboring frequencies [1,2,3]. At the net level, this phenomenon manifests itself as an increase in the cortical region activated by frequencies located on the border of the auditory loss. This phenomenon is analogous to that observed in the somatosensory system [4,5].

Some authors have proposed that phantom perceptions which occur in some subjects after peripheral lesions, might constitute by-products of the neural reorganization processes that are induced by the lesion. This hypothesis is supported, in the somesthetic modality, by the finding of a correlation between phantom limb pain sensation and the amount of cortical reorganization occurring in the somatosensory cortex following amputation or nervous system injury [4,6,7,8]. In the auditory

modality, a similar relationship between tinnitus and tonotopic reorganization in the auditory cortex has recently been indicated by data from Mühlnickel *et al.* [9].

In the light of all these data, a hypothesis that can be put forward to try and further understand the relationship between tinnitus and neural plasticity after peripheral damage is that tinnitus results from the over-representation of a narrow range of frequencies falling in or near the lesioned region of the cochlea. A non-invasive way of testing this hypothesis in humans is inspired from the finding that tonotopic reorganization in the auditory cortex parallels variations in perceptual performance in a frequency-discrimination task [10]. This finding is interpreted as an indication of the fact that increased performance in frequency discrimination is underlain by a finer neural representation of the trained frequency region. Conversely, the over-representation of a given frequency range near the lesion-edge of a steeply-sloping hearing loss is likely to result in increased frequency-discrimination performance in this frequency range [11].

The aim of the present study was to test whether tonal tinnitus is associated to tonotopic cortical reorganization by measuring frequency discrimination performances near to and far away from tinnitus frequency. The hypothesis was that, if tinnitus frequency is over-represented in the auditory cortex, frequency discrimination thresholds should be smaller at and around the tinnitus frequency than at other frequencies.

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Material and methods

Six subjects (2 males, 4 females) aged between 50 and 70 years took part in the experiment. Five had bilateral tinnitus and one had unilateral tinnitus. All subjects had abnormally elevated hearing thresholds. Because none of these subjects had prior experience with psychoacoustic experiments, they were given the opportunity to familiarize with the test material and procedure before actual measurements began.

Discrimination frequency thresholds were measured using a three-interval, two-alternative forced choice (3I-2AFC) procedure. According to this procedure, each trial consisted of the presentation of three intervals, the first and second or third of which contained a tone pip of frequency f ; in the remaining interval, the tone pip had a frequency $f+df$. The subjects task was to indicate via a computer keyboard which interval contained the tone pip with highest pitch. The variable df was reduced by a given factor after two consecutive correct answers; it was increased after any incorrect answer. After 16 reversals in the size of df , the procedure stopped and the threshold was computed as the average of the values taken by df at each of the last 12 reversals. Due to the use of the two down, one up adaptive rule, this threshold corresponded to the 70.7% correct point on the psychometric function. The factor by which df was multiplied or divided was equal to 2 until the fourth reversal, and $\sqrt{2}$ thereafter.

In each listener, at least 5 frequencies were tested. One of these frequencies corresponded to the tinnitus frequency f_{Ti} , which was measured beforehand using a pitch adjustment procedure. The four other frequencies were chosen below (f_1 and f_2) and above (f_4 and f_5) f_{Ti} . At least 3 runs were performed at each test frequency. The frequency discrimination thresholds (FDLs) reported in this study correspond to the average over these 3 runs.

Absolute thresholds were measured at each of the 5 nominal test frequencies using a 2I-2AFC procedure. Consequently, the nominal stimulus level could be set precisely to 30 dB SL at each test frequency in the frequency-discrimination tests.

Four of the subjects with bilateral tinnitus were tested in only one ear (chosen randomly). In two other subjects (one with bilateral tinnitus and the other with unilateral tinnitus), FDLs were measured successively in the two ears.

Results

Figure 1 shows the FDLs and absolute thresholds measured at and around the tinnitus frequencies in two subjects with bilateral tinnitus. In spite of substantial inter-subject variability, a consistent pattern is apparent in the data in the sense that FDLs are smaller at the tinnitus frequency and increase below and above that frequency. The statistical significance of this result was tested using a one way-

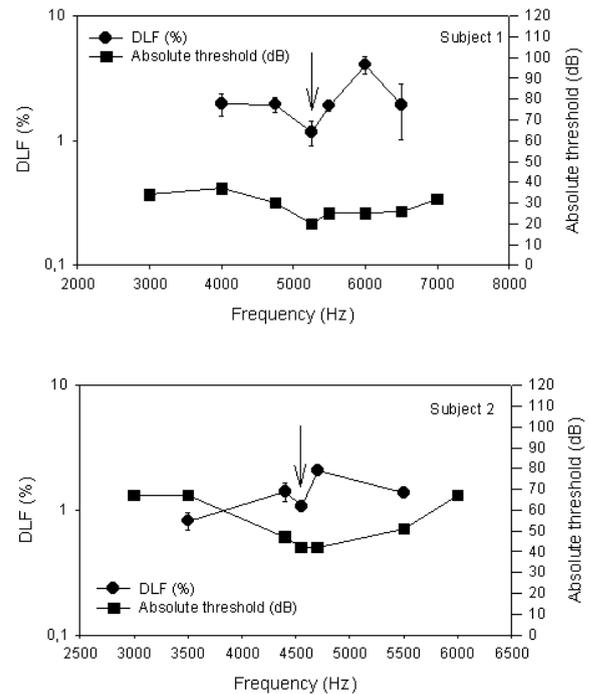


Figure 1 Frequency difference limens (DFLs) (SEM) and absolute threshold for two bilateral tinnitus subjects. FDLs are expressed as the mean frequency difference divided by the reference frequency, and are plotted as a percentage on a logarithmic scale. Arrows indicate the location of the tinnitus frequency.

ANOVA on the log-transformed relative FDLs – i.e. $\log(FDL/F)$ – with the test frequency as repeated-measures factor, in each subject. The results of post-hoc tests revealed that the FDL was significantly lower at the tinnitus frequency (f_{Ti}) than at adjacent frequencies in 4 subjects out of the 6 subjects tested.

Another interesting feature in the data corresponds to an increase in FDLs at frequencies above the tinnitus frequency. This phenomenon, which is particularly apparent in one (subject 1) of the two subjects whose results are shown in Figure 1, was present, to a variable degree, in all the subjects tested.

In the two subjects whose two ears could be tested, a two-way ANOVA with the ear and frequency as factors was performed. Fisher's post-hoc tests were used to gain further insights into the differences in FDLs between the two ears. The FDLs data for these two subjects are shown in Figure 2. In one subject, the tinnitus was bilateral (subject 1); in the other, it was unilateral (subject 6).

In the subject with bilateral tinnitus (subject 1), a significant difference in FDLs was found between the two ears for one frequency (f_4); FDLs were slightly larger in the ear with the lower absolute threshold. However, FDLs varied in a similar way across frequency in the two ears. ANOVA revealed that the interaction between ears and frequencies are not significant ($p > 0.05$). For subject 6 (unilateral tinnitus), the two-way ANOVA revealed a large effect of ear ($p < 0.001$). Surprisingly, while

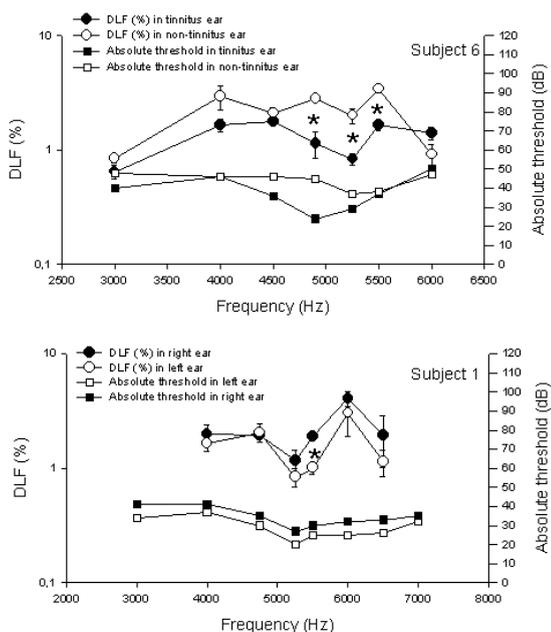


Figure 2 Frequency difference limens (DFLs) (\pm SEM) and absolute threshold in both ears, for one bilateral tinnitus subject and one unilateral tinnitus subjects (*: $p < 0.05$). As in Figure 1, FDLs are expressed as the mean frequency difference divided by the reference frequency, and are plotted as a percentage on a logarithmic scale.

absolute threshold were enhanced in the tinnitus ear (scotoma), the FDLs was lower in this ear compared to contralateral ear non affected by tinnitus and by hearing loss. The two ears differed significantly at fT1, f4 and f5. Furthermore, ANOVA revealed a significant interaction between the ears and frequencies.

Discussion

The main finding of this study is that FDLs were generally smaller at the estimated frequency of the tinnitus than at lower or upper frequencies. The results of numerous earlier studies indicate that FDLs are generally larger in hearing-impaired than in normal-hearing individuals [12,13,14,15,16,17, 18,19,20]. This finding has traditionally been explained in terms of the detrimental effect of coch-

lear damages on the accuracy of the spectral or temporal representations of frequency in the peripheral auditory system [21,22]. However, in a recent study, McDermott *et al.* [11] have demonstrated that although FDLs are on average larger in hearing impaired than in normal hearing subjects, local improvements could be observed near the frequency cutoff of steeply-sloping (“ski-slope”), high-frequency hearing losses. One interpretation advanced by these authors to explain their finding is inspired from neurophysiological data in animals which indicate that after cochlear lesions, cortical regions which were previously excited by certain frequencies, and which are now deprived from peripheral inputs start to respond to neighboring frequencies [3]. The resulting over-representation of a given frequency range in the neural tonotopic map would increase the probability that different frequencies in that range elicit different spatial patterns of neural activity, thereby increasing the likelihood that a frequency difference is detected.

Before elaborating on the agreement between our observations and the interpretation proposed by McDermott *et al.* [11], we must first consider other possible interpretations. A first possible interpretation is that due to loudness recruitment, the loudness of the test stimuli may have been larger when their frequency was close to the frequency of maximum hearing loss than when it was in regions of minimal loss. However, it has been demonstrated that FDLs become largely independent of the stimulation level when this level reaches about 30 dB SL or less, depending on the amount of auditory loss [23]. Since in the present study, the stimuli had an intensity of 30 dB SL, and most of the listeners had elevated hearing thresholds, this phenomenon is unlikely to have significantly affected the measured FDLs.

Another possible interpretation of our result is that, due to variations in absolute threshold across frequencies, the subject’s performance was based on loudness differences, rather than pitch differences between the stimuli to be discriminated. The larger the difference in absolute threshold between the two frequencies of the stimuli, the more marked the loudness difference between these stimuli. Consequently, the fact that the audiogram slope was generally the steepest near the frequency of maximum loss might explain that FDLs were the small-

Table 1

| Subject | Reference frequencies | | | | | | |
|---------|-----------------------|------|------|------|------|------|------|
| | f0 | f1 | f2 | fTi | f4 | F5 | f6 |
| 6 | 3000 | 4000 | 4500 | 4900 | 5250 | 5500 | 6000 |
| 1 | | 4000 | 4750 | 5250 | 5500 | 6000 | 6500 |
| 3 | | 4500 | 5000 | 5250 | 5500 | 6000 | |
| 2 | | 3500 | 4500 | 4550 | 4700 | 5500 | |
| 5 | | 4000 | 4500 | 5000 | 5500 | 6000 | 6500 |
| 4 | | 3000 | 4500 | 5000 | 5250 | 5500 | 6000 |

est around that frequency. However, the prediction that can be made on the basis of this interpretation, which is that variations in FDLs across frequencies should be related to variations in absolute threshold, is not met by the data. There are indeed several instances in the present data of large variations in FDLs over frequency ranges over which absolute thresholds do not vary much, or the converse. Furthermore, there exist data in the literature which clearly argue for a lack of correspondence between absolute thresholds and FDLs by showing that FDLs can differ widely across the two ears of hearing-impaired subjects whose thresholds are identical, or the converse [20]. But probably the most convincing argument for the notion that the variations in FDLs across frequencies that were observed in the present study cannot be explained in terms of absolute thresholds comes from the observation of the results of subject 6. In this subject indeed, FDLs were found to be altered in the ear contralateral to the tinnitus ear, in which the absolute threshold curve was flat. Furthermore, in subject 1, FDLs were deteriorated at frequencies further away from the tinnitus frequency while hearing thresholds stay quite similar between these frequencies. In conclusion, the decreased FDL observed in our study is very unlikely to be related to increased loudness cues because of the hearing loss.

Having ruled out alternative interpretations, we may now consider in more details the interpretation of our results in terms of central auditory system plasticity. The present results are in good general agreement with the results of McDermott *et al.* [11]. However, here, the decreased FDLs were not systematically observed at frequencies located near to the audiometric edge, as was the case in McDermott *et al.*'s study [11]. This difference might be explained by the different types of hearing losses in the two studies: in McDermott *et al.*'s [11] study, the hearing losses were more steeply sloping and they were deeper than in the present study. If tonotopic cortical reorganization occurs at frequencies at which the contrast in absolute threshold reaches a critical value, it will occur closer to the audiometric edge in subjects with steeply-sloping hearing losses.

Another finding of the present study which can be thought of as resulting from central reorganization processes consists of the relative increases in FDL at frequencies further away from the tinnitus frequency. This result may be explained by assuming that neural resources devoted to the processing of auditory stimuli are limited, and once reallocated to the processing of a given frequency range, they become unavailable for the processing of stimuli falling outside this range. Interestingly, the comparison of the FDLs measured in the two ears of one of our subjects (subject 6) who had a unilateral tinnitus and exhibited a typical audiogram notch at the tinnitus frequency in her tinnitus ear but a roughly flat audiogram in her contralateral ear, suggests that this neural reallocation phenomenon might take place not only across frequencies in a

given ear, but also across ears. Indeed, in this subject, FDLs were found to be overall smaller in the tinnitus than in the non-tinnitus ear. Furthermore, a deterioration in FDL in the non-tinnitus ear was found to correspond to the improvement in FDL observed around the tinnitus frequency in the tinnitus ear. In contrast, in the subject with bilateral tinnitus in whom the two ears could be tested (subject 1), the shape of the FDL curves proved to be very similar between the two ears.

In conclusion, the present results suggest that the frequency of tinnitus falls in a frequency range to which an increased number of neurons respond. This view is consistent with the notion that tinnitus originates in aberrant neural activity in the auditory system [24,25]; the increased number of neurons responding to a given frequency range might either be the origin of this aberrant neural activity, or it might contribute to emphasize its representation at the level of the auditory cortex, thereby facilitating its access to consciousness. It may further be suggested that the occurrence of tinnitus in some subjects but not others might, like phantom limb pain, be related to the amount of underlying neural reorganization. The present results are also in partial agreement with results from Mühlnickel *et al.* [9] who recently provided evidence for cortical auditory reorganization in tinnitus subjects using magnetic source imaging. One main difference between these results and those obtained here comes from the fact that while all our subjects had a hearing loss at or near the tinnitus frequency, the results of Mühlnickel *et al.* [9] were obtained in subjects who had apparently no hearing loss. However, because in the latter study, the hearing thresholds were estimated using relatively large frequency steps, it remains possible that the subjects in fact had focal hearing losses near the tinnitus frequency.

Finally, the present results further underline the potential interest of tinnitus-reeducation approaches based on perceptual training at frequencies close to the tinnitus frequency. Frequency-discrimination training in the frequency range where FDLs are deteriorated – i.e. in the frequency band supposedly “abandoned” by those neurons that “invaded” the frequency range of tinnitus; might alleviate tinnitus by contributing to restore a normal tonotopic organization. Further work is required to test this possibility.

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What the MRA has been showing in pulsatile tinnitus?

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Objectives: Pulsatile tinnitus (PT) is the perception of a rhythmic sound, synchronous with the heartbeats. It is frequently associated to identifiable causes, thus deserving a special attention regarding the etiologic diagnose. One of the most important causes of pulsatile tinnitus is the paraganglioma, a vascular tumor that appears as a reddish retrotympenic mass. However, when the tympanic membrane is normal, it is essential to consider other diagnoses, such as arteriovenous malformations, fistulas, intracranial aneurysms, high/dehiscent jugular bulb, persistent stapedial artery and others. The authors intended to evaluate the findings in magnetic resonance angiography (MRA) possibly related to the etiologic diagnosis of pulsatile tinnitus with normal otoscopy.

Methods: From January 1995 to March 1999, 26 patients with pulsatile tinnitus and normal otoscopic exam were prospectively evaluated. There were 21 females and 5 males, whose ages ranged from 25 to 71 years (average 45.84 years). All patients underwent a complete audiometric evaluation, a computerized tomography scan, and a magnetic resonance imaging (MRI) exam with complementary magnetic resonance angiography (MRA).

Results: MRA showed vascular alterations in 20 of the 26 cases (76.9%), including 2 aneurysms and 1 intracranial hypertension. Interestingly, 16 patients (61.5%) showed one or more variations of the regular vascular anatomy of the skull base as a single finding. The vertebral artery was affected in 11 of the 16 cases (68.75%).

Conclusions: The authors confirm the MRA as an excellent screening for patients with pulsatile tinnitus and point out to the importance of making the etiologic diagnosis, suggesting the variations of the vascular anatomy of the skull base as one of the possible etiologies.

Introduction

Although rare in the daily practice, pulsatile tinnitus (PT) deserves a special attention from otorhinolaryngologists. It is a rhythmic auditory sensation, synchronous with the heartbeat [1], and frequently associated to identifiable causes. PT mainly originates in vascular structures (venous or arterial vessels) as a result of flow turbulence due to increased blood volume or change in the vessel lumen [2,3,4,5]. When such alterations are close to the skull base, they may produce such auditory sensation [3,5].

The jugular and tympanic paragangliomas are the best known causes of PT. However, these vascular tumors often present with a reddish retrotympenic

mass [6] in the physical exam, which strongly suggests the correct diagnosis [2,7]. A greater challenge occurs when the tympanic membrane is normal. Then, other etiologies of PT must be considered, such as dural malformation, arteriovenous fistulas, intra- or extracranial aneurysms, high or dehiscent jugular bulb, persistent stapedial artery, among others [3,5,6,8,9,10].

Jacobson, in 1882, was the first to describe a case of auditory sensation of cranial murmur associated to atherosclerosis [4]. Since 1936, many authors have described cases of PT associated to several etiologies, such as vascular abnormalities [10], venous hum [11], high jugular bulb and dehiscent internal carotid artery [3,7] and tumors of the cerebellopontine angle. In 1984, Vallis and Martin described the arteriovenous malformations as the most important etiology of PT [7]. As far as we concern, there is no report in the literature regarding the correlation between PT and anatomic variations of the arteries close to the skull base.

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Summarized vascular anatomy of the skull base

Within the posterior circulation of the skull, anatomy takes center stage. More than in any other region, accurate diagnosis depends on an intimate familiarity with the brain and vascular anatomy [12]. The vascular supply of the posterior circulation is from the paired subclavian-vertebral arteries, which join intracranially to form the basilar artery, which in turn bifurcates into the paired posterior cerebral arteries.

Extracranial large arteries

The subclavian arteries give rise to their first branches, the vertebral arteries (VA), which commonly present variations [13]. The vertebral arteries, more often the left, may arise directly from the aortic arch (about 8%), while the right VA may originate directly from innominate artery. In very rare cases, either VA can arise from the common carotid artery on the same side. The VAs are often asymmetric: in about 45% of individuals, the left VA is larger; in 21%, the right VA is dominant, and in 34% both arteries are of about equal size [14]. One VA may be atretic or very hypoplastic.

Intracranial large arteries

The intracranial portion of the vertebral arteries (ICVA) is often asymmetric; one may be two to three times the size of the contralateral VA, with the left ICVA more often the larger. The 4 most important branches of ICVAs are the anterior and posterior spinal arteries, posteroinferior cerebellar arteries (PICAs) and direct lateral medullary branches. The PICAs are the largest and yet the most variable of the ICVA branches [15]. The most distal segment of the ICVAs forms at a different time embryologically, and this segment is often hypoplastic or even absent. In that case, angiograms show that the ICVA seems to end in PICA, and the contralateral ICVA is usually larger and responsible for the major basilar artery (BA) supply. This situation is often referred to as "basilarization" of one ICVA. Usually, when the left ICVA is dominant, the BA deviates to the right, while it deviates to the left when the right ICVA is dominant. In only 25% of patients does it have a perfectly straight course [16]. The main branches of the BA are the anteroinferior cerebellar arteries (AICAs). The size of the PICAs and AICAs on each side is often reciprocal. Either can be very hypoplastic or absent, in which case the PICA or AICA supplies the entire territory on that side. The posterior cerebral arteries (PCAs) originate from the terminal bifurcation of the BA. In about 10% of individuals, a fetal pattern persists in which the PCA essentially originates from the internal carotid artery (ICA), and the proximal segment of the PCA from the BA is hypoplastic [17]. One PCA can be unusually large (29%) or small (24%).

Since the establishment of magnetic resonance angiography (MRA) technique, many vascular abnormalities have been identified, representing a great advance for many areas, including Otoneurology. Considering the high incidence of identifiable and treatable causes of PT, the correct etiologic diagnosis becomes fundamental in its evaluation. Therefore, the objective of the present study was to evaluate the effectiveness of the MRA in the establishment of the etiologic diagnosis of the pulsatile tinnitus.

Methods

This prospective study was conducted at the Tinnitus Ambulatory of ENT Department of University of São Paulo, from January 1995 to March 1999. During this period, 26 patients with PT and normal otoscopy were evaluated, 21 females and 5 males, whose ages ranged from 25 to 71 years (average = 45.84 years).

All patients underwent a complete head and neck evaluation. Exclusion criteria consisted of clinical or radiological evidences of paragangliomas (reddish mass in otoscopy or by CT scan) and of venous hum (specific changes in tinnitus with head rotation and disappearance with smooth compression of jugular vein). In order to discard systemic causes of PT, such as anemia and hyperthyroidism, a clinical investigation was always accomplished, emphasizing the following general exams: complete blood count, glucose test, cholesterol, triglycerids, thyroid hormones and serology for syphilis.

Eventually, the 26 patients enrolled in the study were submitted to a magnetic resonance imaging (MRI) exam with complimentary magnetic resonance angiography (MRA). Such exams were always accomplished by the same radiologist, using the team-of-flight (TOF—3D) spin-echo technique, with sequences weighed in T1 and T2. Axial acquisitions and sagittal reconstructions were performed, without the use of endovenous contrast.

Results

Epidemiologic data revealed a significant preponderance of females when compared to males, in a rate of 5.6:1. The symptom has been present for less than 2 years in 8 patients; from 2 to 5 years in 7, and for more than 5 years in 2 patients.

The clinical investigation was normal in all patients, as well as the temporal bone CT scans. All MRIs were normal, but one (M.J.S.), which showed dilatation of cerebral ventricles due to intracranial hypertension.

The results of MRA in each patient are summarized in Table 1. Twenty out of the 26 exams (76.9%) presented alterations of the vessel lumen or of the velocity of the blood flow, including 2 patients with intracranial aneurysms and 1 with intracranial hypertension due to Arnold-Chiari syndrome. Only 6 patients presented normal exams (23%), not allowing the etiologic diagnosis.

Considering the 20 patients with altered MRA, 16 (61.5%) presented with at least one variation of the vascular anatomy of the skull, showing a close correlation with the side of PT in most cases. The vertebral artery was the most involved, presenting itself with hypoplasia, agenesis or dominance in 11 cases (68.7%), as seen in Table 1.

Discussion

Pulsatile tinnitus (PT) is generally the otologic manifestation of a blood flow abnormality of the temporal bone. Synchronous to the cardiac pulsation [1,7,18], PT can reach high intensity and become a reason of psychological disability for some patients [3,19]. This kind of tinnitus is a common reason for indication of an image exam of this region [2,6].

The importance of investigating PT is justified by its higher association with identifiable and treatable causes when compared to the common kind of subjective and non-pulsatile tinnitus. Besides, the misdiagnosis can be catastrophic, once it may be related to intracranial diseases, such as aneurysms and tumors [18,19].

The most common causes of PT described in the literature are the dural arteriovenous malformations and fistulas [3,5,6,8,9,10], as well as the paraganglioma (tympanicum, jugulare or jugulotympanic glomus) [2,7]. The paraganglioma presents with a vascular retrotympanic mass, which is an important sign to the physician, strongly suggesting the diagnosis [6].

The present study just considered patients with normal otoscopy. According to our results, the MRA was able to identify abnormalities related to the cause of the pulsatile tinnitus in 76.9% of the patients (20/26). Interestingly, we noticed that the most common established cause of PT was the anatomic variation of the vascular anatomy of the skull, which has not been described in the searched literature.

According to Brodal "In Neurology, a knowledge of structural features is perhaps more important for an understanding of function under normal and pathological conditions than in any other branch of medicine. The determination of the site of the lesion is therefore an important link in understanding the nature of the disease" [20]. According to Lasjaunias; Berenstei, "the specific need to understand the variations and variabilities of the vascular

Table 1 Results of MRA in the 26 patients with pulsatile tinnitus and normal otoscopy. See the correlation with the side of tinnitus

| N | Initials | Age | Sex | Duration | Side | Severity | Magnetic resonance angiography |
|----|------------|-----|-----|------------|-------|----------|--|
| 1 | P.S.R. | 43 | M | <1 year | L | Moderate | Agenesis of right VA |
| 2 | M.G.F. | 37 | F | 3-5 years | R | Severe | Aneurysm of right ICA at the exit of the ophthalmic artery |
| 3 | A.M.B. | 54 | F | <1 year | R | Severe | Aneurysm of right supraclinoid ICA in the exit of the posterior communicant artery |
| 4 | G.C.S. | 71 | F | 1-2 years | R | Severe | Basilarization. Blood flow is slow |
| 5 | D.A.S. | 25 | F | 2-3 years | L | Severe | Discreet dominance of the left VA |
| 6 | G.F. | 48 | M | 3-5 years | L | Severe | High left carotid artery |
| 7 | A.M.S. | 58 | M | 1-2 years | L | Severe | Hypoplasia of left A1, basilarization, left VA dominant with projection to the left cerebellopontine angle |
| 8 | A.M.S.F. | 43 | F | 1-2 years | R | Moderate | Hypoplasia of left VA |
| 9 | D.S.A. | 32 | F | 3-5 years | R | Moderate | Hypoplasia of right VA |
| 10 | M.L.S. | 50 | F | <1 year | L | Severe | Hypoplasia of right VA, dominance of left VA |
| 11 | C.T.R. | 63 | F | <1 year | L | Mild | Hypoplasia of right vertebral |
| 12 | M.M. | 51 | M | 2-3 years | Malar | Mild | Hypoplasia of right vertebral artery |
| 13 | L.B.K. | 29 | F | 3-5 years | R = L | Moderate | Hypoplasia of the left VA, right PICA dominant, close to VII and VIII nerves |
| 14 | M.J.S. | 35 | F | 5-10 years | R | Severe | Intrac hypertension, hydrocephalus, seringohydromyelia, cerebelar tonsil below the magno forame (Chiari I) |
| 15 | Z.P.M. | 51 | F | 2-3 years | R = L | Severe | Left posterior cerebral artery origins from ICA (fetal pattern), hypoplasia of left VA |
| 16 | N.B. | 53 | F | >10 years | L | Severe | Left vertebral dominant, hypoplasia of posterior communicant artery. Venous: hypoplasia of left transverse sinus |
| 17 | M.V.R. | 48 | F | 2-3 years | L | Moderate | Mild basilarization, left PICA dominant, thick right AICA dominant |
| 18 | M.D.S. | 37 | F | 1-2 years | R | Moderate | Mild sinuosity of the basilar artery |
| 19 | M.F.A. | 32 | F | <1 year | R = L | Severe | Mild vascular blush in the projection of left ear |
| 20 | G.F.O. | 53 | F | 1-2 years | R = L | Severe | Multiple murals irregularities in the petrous carotids arteries. Hypoplasia of left A1, basilarization |
| 21 | S.O.C. | 32 | F | 3-5 years | L | Severe | Normal |
| 22 | M.D.S.R.S. | 37 | F | <1 year | R = L | Severe | Normal |
| 23 | T.S.S. | 43 | F | 2-3 years | Head | Severe | Normal |
| 24 | I.V. | 45 | F | 1-2 years | L | Severe | Normal |
| 25 | P.C.P. | 52 | M | 1-2 years | L | Moderate | Normal |
| 26 | J.M.C. | 70 | F | 1-2 years | R > L | Moderate | Normal |

Note: M = male; F = female; R = right; L = left; VA = vertebral artery; ICA = internal carotid artery

anatomy and its applications has increased. The variability, although 'normal', represents an increased rigidity of the system. It may remain compatible with function for a long time, but a minimal constraint may betray its limited flexibility. Thereafter, the variation becomes 'abnormal' and symptomatic" [21].

Evaluating the MRA of the 16 patients with any alteration, we noticed that 11 (68.7%) presented only with variations of the arterial vascular anatomy of the skull. There is no previous report in the literature about the correlation between such anatomical variation and the pulsatile tinnitus. Once this finding is very relevant, we can hypothesize that the turbulence occurred during the passage of the blood flow through such altered vessels can promote tinnitus appearance. For example, the patient D.A.S., with PT in the right ear and hypoplasia of the right vertebral artery might be explained, in the absence of other causes, due to a turbulent flow in such a narrow vessel. The same can be said in relation to the patient L.B.K., with bilateral pulsatile tinnitus and MRA showing dominance of right PICA and hypoplasia of the left VA.

Once the anatomic variation is congenital and the PT seems to appear only in adulthood, we still need to find out the predisposing factors that trigger the tinnitus appearance. As said before, the variation may remain compatible with function for a long time, but a minimal constraint may betray its limited flexibility. Thereafter, the variation becomes "abnormal" and symptomatic [21]. Probably future studies will solve this question.

Radiological investigation: Some considerations

Clinical diagnosis of PT is based on a complete neurotological evaluation, which includes clinical history, complete physical exam, with special attention to the otoscopic exam, auscultation of the external auditory canal and adjacent areas, palpation of the high cervical area and pre-auricular region [1,5]. It is important to evaluate an eventual papiledema, what leads to the diagnosis of benign intracranial hypertension syndrome [5]. It is described in the literature the use of a modified electronic stethoscope, the "auscultear", to help in evaluation of the PT, mainly in objective tinnitus [22].

Radiological investigation is of the utmost importance for the establishment of etiologic diagnosis. Computed tomography (CT) allows diagnosis of bone alterations associated to vascular anomalies [1,6]. The high resolution CT is the appropriated exam to be requested to patients with retrotympenic masses, allowing such diagnoses: paragangliomas, aberrant internal carotid artery, and abnormalities of the jugular bulb. Even though, it can not detect arteriovenous malformations or arteriovenous fistulas of the dura, which are the most important causes of PT, especially in the presence of normal otoscopic findings [1].

Angiography has a larger sensibility, allowing the diagnosis of arteriovenous fistulas and intrinsic vascular anomalies. On the other hand, it is an invasive exam, with a considerable related morbidity index in some series [6]. Thus, it should not be used as a screening exam, being indicated just in limited cases such as pre-operative evaluation and/or embolization, evaluation of collateral circulation with possibility of vessel occlusions, and therapeutic embolizations [3,5,7,8,18,19]. Until recently, radiological investigation of PT was based on the accomplishment of the CT scan associated with angiography [5,6]. Generally, angiography has been restricted to those cases when MRA is normal, once it may detect small abnormalities not shown in MRA.

Due to its poor resolution for vascular and bone structures, the magnetic resonance image is of limited benefit when used alone. Without contrast, it is not enough to differentiate some vascular tumors from arteriovenous malformations nor to identify regions of vascular compressions, limiting its use in patients with PT. When contrasted with gadolinium, MRI can establish the diagnosis of paraganglioma [6]. In our study, only one MRI showed alterations correlated to the diagnosis, not being a proper exam for evaluation of PT.

The establishment of the MRA technique offers additional information, superior to MRI alone, substituting the angiography in almost the totality of cases. It increases the ability in the diagnosis of lesions responsible for PT, mainly dural arteriovenous malformations and fistulas [1,5,6]. It is also extremely useful in the evaluation of vascular tumors, with special attention to paragangliomas. It also allows differentiating vascular neoplasms from those with less vascular components, facilitating the differential diagnosis between meningioma and schwannoma. Thus, its superiority is obvious in precise neurovascular evaluations, demonstrating small vascular alterations, as well as occasional vascular compressions [23].

Dietz, in 1993, compared MRI and MRA in the evaluation of 49 patients with PT, noticing vascular lesions in 28 cases, which were demonstrated better (46%) or just visualized (36%) in the MRA [7]. This technique represented great impact in the evaluation of patients with PT and normal otoscopic exam, allowing the precise etiologic diagnosis and the adequate treatment of the patient.

MRA allows screening of patients with PT through only one radiological exam [6]. Nowadays, it should be used as first choice in these patients, be the tinnitus objective or subjective, accompanied or not with retrotympenic mass, cervical lesions or cranial nerve deficits [11]. In the present study, MRA allowed the etiologic diagnosis in 76.9% of the cases, with a good correlation between localization of tinnitus and the side of the identified abnormality. Thus, it should be considered as a practical, safe and effective screening test in such cases, allowing the diagnosis through a single radiological exam. The authors wish to remind the variations of the vascular anatomy of the skull as a possible cause of pulsatile tinnitus.

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Growth of fMRI activation with stimulus level in the inferior colliculi: Implications for understanding tinnitus-related abnormalities

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Functional magnetic resonance imaging (fMRI) provides a means for studying the pathophysiology of tinnitus in humans by enabling brain activation to be spatially mapped non-invasively. Our previous data showed abnormally asymmetric fMRI activation in the inferior colliculi (ICs) of audiometrically normal patients with tinnitus lateralized to one ear when stimulated with binaural masking noise at 55 dB SL. This asymmetry was due to abnormally low fMRI activation in the IC contralateral to the tinnitus percept. We have proposed two models that could account for the observed tinnitus-related abnormalities: “Saturation” and “Physiological Masking”. Both assume abnormally elevated neural activity (“tinnitus-related” activity) in the IC. By the Saturation model, abnormally low fMRI activation results because neural activity reaches a maximum during stimulation. By the Physiological Masking model, abnormally low activation results because of a reduction in tinnitus-related activity corresponding to acoustic masking. More data is required to distinguish between these two models.

This study is the first step in this direction. We first demonstrate that in subjects without tinnitus fMRI activation, on average, increases linearly with increasing stimulus level (from 35 to 75 dB SL). We then show how these data can be combined with our present knowledge about tinnitus-related abnormalities in the IC to place constraints on the underlying mechanisms of tinnitus. Finally, we outline an approach that will enable us to test the Saturation and the Physiological Masking models in tinnitus patients using activation vs. level functions.

Introduction

Functional magnetic resonance imaging (fMRI) enables sites of brain activation to be localized in human subjects [1,2,3]. It is well-suited for studying the pathophysiology of tinnitus because it is non-invasive and is applicable to individual subjects which is critical considering the heterogeneity of the tinnitus population. fMRI has millimeter spatial resolution and enables imaging of the auditory system from cochlear nucleus to cortex [4], thus providing an opportunity to detect tinnitus-related

abnormalities throughout the central auditory pathway.

The present study builds on our recent results showing that fMRI can provide an objective measure of lateralized tinnitus [5,6]. Specifically, we found that subjects with lateralized tinnitus and normal hearing thresholds showed abnormally asymmetric fMRI activation in the inferior colliculi (IC) when stimulated with broadband masking noise at 55 dB SL (Figure 1, right). This abnormality was identified by comparing activation in the tinnitus subjects to that of audiometrically-matched control subjects without tinnitus (Figure 1). The abnormal asymmetry for lateralized tinnitus subjects was such that, on average, there was abnormally low fMRI activation in the IC contralateral to the tinnitus percept.

We have proposed two possible models to explain

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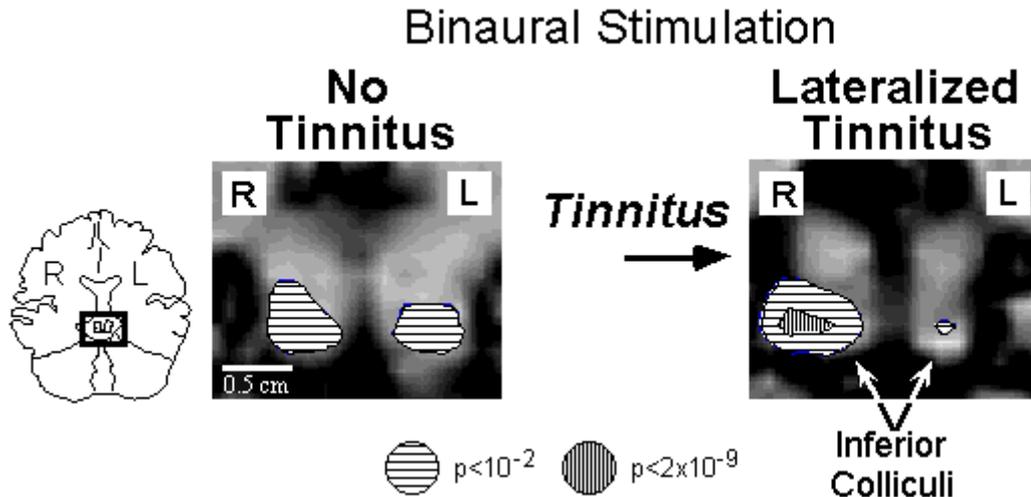


Figure 1 fMRI activation maps demonstrating our previous finding: abnormally asymmetric activation in the inferior colliculi of lateralized tinnitus subjects [5]. Activation (hatched areas) was in response to binaural broadband noise at 55 dB SL. Activation maps indicate the result of a t-test comparison of functional images acquired while the noise stimulus was on vs. while it was off (horizontal hatching – $p < 0.01$; vertical hatching – $p < 2 \times 10^{-9}$). In each panel, the activation map is superimposed on a grayscale anatomical image acquired during the same imaging session. Area of each panel corresponds to the rectangle on the schematic image at left.

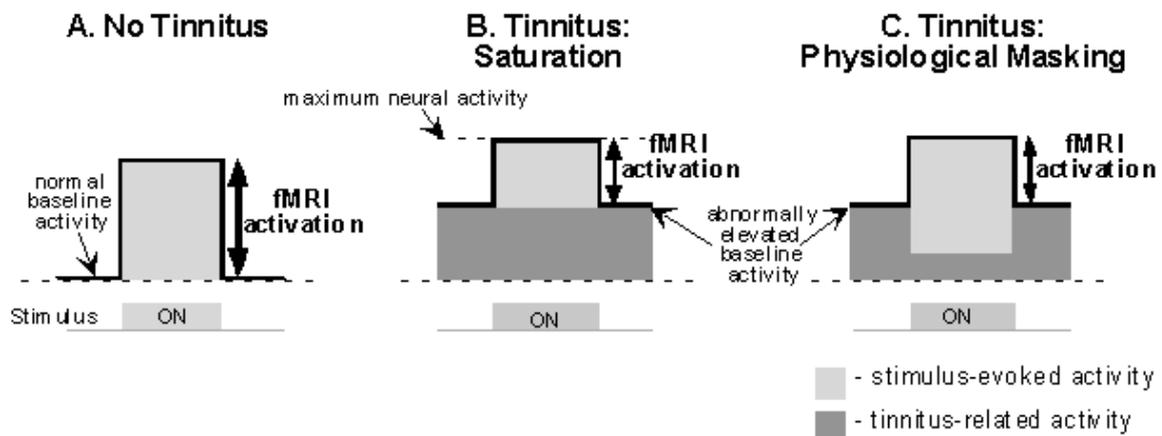


Figure 2 Saturation and Physiological Masking models. In subjects without tinnitus (A), neural activity increases when an acoustic stimulus is turned on (stimulus-evoked activity, light gray area). In subjects with tinnitus, elevated baseline activity (tinnitus-related activity, dark gray area) is assumed for both models (B and C). By the Saturation model (B), fMRI activation is abnormally low because neural activity reaches a maximum when the stimulus is turned on. By the Physiological Masking model (C), fMRI activation is abnormally low because tinnitus-related activity decreases when the tinnitus percept is masked by the stimulus. For simplicity, (C) illustrates a case where there is tinnitus masking only during stimulation (i.e., no residual inhibition). If there were residual inhibition, tinnitus-related activity during stimulus off periods would be reduced in proportion to the degree of residual masking.

the abnormally low activation seen in lateralized tinnitus subjects [5]. Both models assume abnormally elevated baseline neural activity in the IC (“tinnitus-related” activity, Figure 2B, C, dark gray area). To understand these models, it is important to realize that fMRI activation indicates a *change* in neural activity between the stimulated and unstimulated conditions, not an absolute level. In one model (Saturation model, Figure 2B), abnormally low fMRI activation results because tinnitus-related activity leaves little room for a further increase in the stimulus-evoked activity (light

gray area) before reaching a maximum. The other model (Physiological Masking model, Figure 2C) assumes a decrease of tinnitus-related activity corresponding to the masking of the tinnitus percept (i.e. a decrease in tinnitus loudness during auditory stimulation). Thus, fMRI activation, the difference between stimulated (stimulus-related plus *reduced* tinnitus-related neural activity) and non-stimulated (tinnitus-related activity) conditions, is abnormally low. The present study takes a first step toward distinguishing between these two models.

Here, we determined the dependence of IC

activation on stimulus level in individuals without tinnitus. Our motivation was to determine whether activation increases with increasing stimulus level or whether it saturates because these possible outcomes have different implications for the proposed models.

Methods

Eight subjects without tinnitus were imaged in ten sessions. Four subjects had normal thresholds (≤ 25 dB HL) and four others had normal thresholds for all but one audiometric frequency (30 dB HL). Written, informed consent was obtained from each subject. This study was approved by institutional committees on the use of human subjects at the Massachusetts Eye and Ear Infirmary, Massachusetts General Hospital, and Massachusetts Institute of Technology.

Subjects were imaged in two series of experiments with slightly different methodologies which included the use of different scanners. For both series, subjects were imaged using a 1.5 Tesla scanner and a head coil (General Electric). For series 1, the scanner was equipped for echo-planar imaging by GE, and for series 2 by ANMR Inc. Pillows were snugly packed around the subject's head in the head coil to minimize head movement.

In all experiments, a single slice was anatomically and functionally imaged. A single slice rather than multiple slices was imaged to reduce the acoustic background noise produced by the scanner. The imaged slice passed through the ICs and either Heschl's gyri (Series 1) or the medial geniculate bodies (Series 2). Anatomical images were T1-weighted (1.5 \times 1.5 mm in-plane resolution, 7 mm slice thickness). Functional image acquisitions (3.1 \times 3.1 mm in-plane resolution, 7 mm thickness, asymmetric spin echo, TE = 70 ms, τ offset = -24 or -25 ms) were synchronized to the subject's cardiac cycle. Images were acquired every other heart beat resulting in the interimage interval (TR) of approximately 2 sec. Post acquisition, image signal strength was corrected to account for variations in TR caused by fluctuations in heart rate. This "cardiac gating" technique increases the detectability of activation in the inferior colliculi over that obtained with a fixed TR [7].

Stimuli were delivered under earmuffs that attenuated scanner noise by approximately 30 dB [8]. The acoustic transducers were housed either under the earmuffs (Series 1) or in a shielded box adjacent to the scanner (Series 2). In the latter case, the transducer outputs were coupled to the earmuffs via air-filled tubes.

The stimulus was binaural broadband noise presented in a typical fMRI paradigm: the stimulus was repeatedly turned on for 30 s. and off for 30 s. while functional images were acquired. Four "stimulus on/stimulus off" repetitions constituted a functional imaging "run". For each run, stimulus level during the "on" periods was the same (35,45,55,65 or 75 dB SL). The number of runs at each level was three

(8 imaging sessions), two (1 session) or one (1 session). At least three levels of broadband continuous noise were used in every imaging session. The order of stimulus levels was randomized in each session.

During functional imaging, subjects performed a task comparable to that performed by tinnitus subjects in our previous experiments [5]. Previously, the tinnitus subjects indicated the loudness of their tinnitus by turning a knob to control the number of lights illuminated (no illuminated lights indicated "no tinnitus", ten lights indicated the loudest tinnitus ever experienced). In the present study, subjects were instructed to turn all the lights on when the noise stimulus was off and turn the lights off when the stimulus was on (i.e., manipulate the lights as if they had tinnitus which was completely masked by the stimulus).

The functional imaging data were analyzed to generate maps of activation and to quantify activation in the inferior colliculi. First, the data for all runs were normalized to the same average signal level and corrected for linear or quadratic drifts in signal level over the course of the run. For each imaging session, runs corresponding to the same stimulus level were concatenated and corrected for head movement (using SPM95). Activation maps were then computed for each stimulus level by comparing image signal strength during stimulus on and off conditions on a voxel-by-voxel basis using an unpaired t-test. To quantify activation, percent signal change for the voxel with the lowest p-value in each IC was computed as:

$$[(S_{\text{on}} - S_{\text{off}}) / (\text{average of } S_{\text{on}} \text{ and } S_{\text{off}})] \times 100,$$

where S_{on} and S_{off} are the mean signal during the stimulus on and off conditions, respectively. There was no statistically significant difference in percent signal change for Series 1 as compared to Series 2 ($p = 0.93$ for 55 dB SL; $p = 0.06$ for 75 dB SL, t-test), so data from the two series were combined.

Results

Subjects without tinnitus consistently showed an overall increase in activation with increasing stimulus level. This trend is illustrated qualitatively by the activation maps for one subject in Figure 3, and by the plots of percent signal change vs. level for each IC of each subject and imaging session (Figure 4A). Of the 20 curves in Figure 4A, 12 show a monotonic increase in percent signal change with increasing level (see also Figure 3, right IC). Linear fits to these curves all had positive slopes, indicating an overall trend of increasing activation with increasing level.

Percent signal change averaged across subjects, imaging sessions and ICs increased monotonically with increasing stimulus level (Figure 4B). Mean percent change increased from 0.45% at 35 dB SL (the lowest stimulus level studied) to 1.2% at 75 dB SL (the highest level studied). This difference was statistically significant with $p < 0.001$ (unpaired t-test). The mean percent signal change vs. level data were well fit by a straight line (chi square

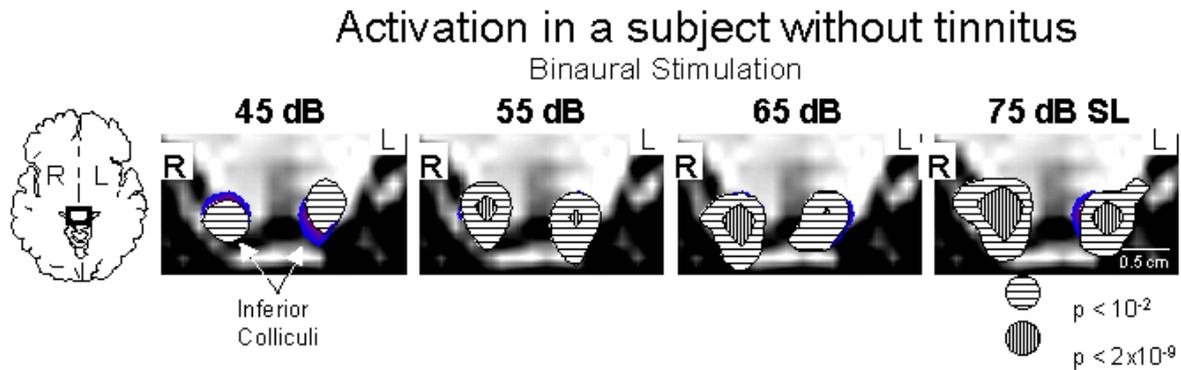


Figure 3 IC activation in response to binaural broadband noise presented at 45, 55, 65, and 75 dB SL. Each panel shows an fMRI activation map (hatched areas) superimposed on a grayscale anatomical image. The area shown in each panel is indicated on the diagrammatic brain slice at left. For the activation maps, hatching indicates the results of a t-test comparison of image signal strength during noise “on” and “off” periods (i.e., horizontally hatched areas where $p < 10^{-2}$, and vertically hatched areas where $p < 2 \times 10^{-9}$). The activation maps computed from the functional data (3.1×3.1 mm resolution) was interpolated for display on the anatomical image (1.5×1.5 mm resolution).

Activation vs. Stimulus Level in subjects without tinnitus

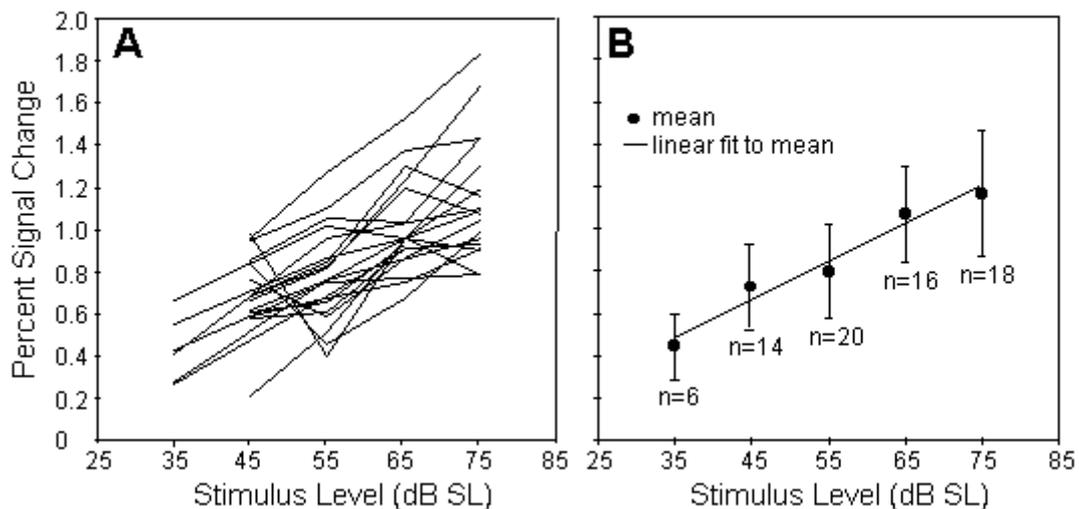


Figure 4 Percent signal change vs. stimulus level for subjects without tinnitus. A. Individual activation vs. level functions for each of the 20 ICs (10 imaging sessions). B. Mean percent signal change for each level (filled circles); error bars indicate one standard deviation above and below the mean. The solid line is a chi square fit to the data (slope = $0.0185\%/dB$ SL; intercept = -0.179%). There was no statistically significant difference between the left and right IC activation at any level ($p > 0.14$), so data from the two ICs were combined for calculations of the mean. The number n below each mean indicates the number of available data points for each level.

fit, $P = 0.97$ [9]), indicating that, on average, IC activation increased linearly with increasing level.

Discussion and conclusion

Our fMRI results indicate that total neural activity in the ICs of normal hearing subjects without tinnitus increases with increasing broadband noise level (Figure 4). Since, to our knowledge, this is the first study examining the dependence of fMRI activation on stimulus level subcortically, these data provide new information about the human auditory

system in general and serve as a basis for studies of tinnitus-related abnormalities.

Activation vs. level functions for tinnitus subjects: predictions

Combining our non-tinnitus data with the Saturation and Physiological Masking models leads to predictions of activation vs. level functions for tinnitus subjects. Figure 5 shows hypothetical activation vs. stimulus level functions for tinnitus subjects and the linear fit to our data from subjects without tinnitus (solid line). The short-dashed line

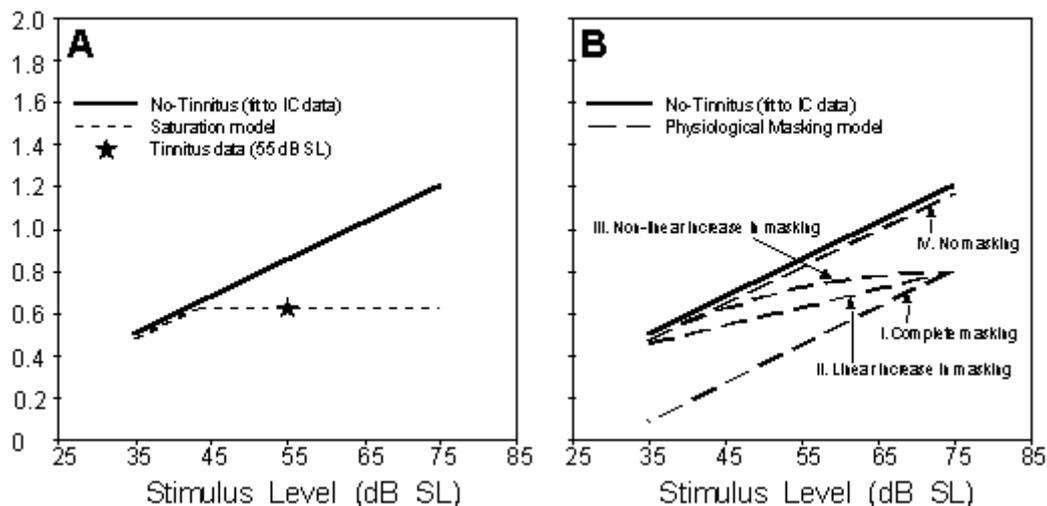


Figure 5 Hypothetical level functions for tinnitus patients: predictions for Saturation (A) and Physiological Masking Models (B). The solid line is the linear fit to the data in subjects without tinnitus from Figure 4. A. The short-dashed line is a prediction for the Saturation model. The star indicates the mean percent signal change in the IC from lateralized tinnitus patients stimulated at 55 dB SL [6]. B. The long-dashed lines are a few possible predictions for the Physiological Masking model: I. Prediction for complete masking of the tinnitus percept at all level; II. Prediction for the linear increase in masking of the tinnitus percept as stimulus level increases; III. Prediction for a non-linear increase in masking of the tinnitus percept as the stimulus level increases; IV. Prediction for no masking of the tinnitus percept for any stimulus level.

shows a prediction from the Saturation model (Figure 5A), in which fMRI activation has a normal growth with level until it saturates at a level lower than the non-tinnitus activation would because the abnormally elevated, tinnitus-related, baseline activity (Figure 2B) leaves little room for neural activity to grow before it reaches a maximum. Our assumption is that tinnitus-related activity does not change with the masking of the tinnitus percept for the Saturation model, and therefore, this model's prediction is independent of variations in tinnitus masking with level. For the Physiological Masking model, however, we assume that tinnitus-related activity is reduced during stimulation to the degree that the tinnitus percept is masked. Therefore, predictions for the Physiological Masking model will depend on the masking of the tinnitus percept vs. level function which is unique to each tinnitus patient. Figure 5B illustrates predictions of the Physiological Masking model (long-dashed lines) for a few possible tinnitus masking vs. level functions. Curve I shows the case in which masking of the tinnitus percept is complete during stimulation at all stimulus levels and there is no residual inhibition. This curve is parallel to and below the non-tinnitus curve because the degree of reduction of the tinnitus related activity is constant across levels for complete masking. Curve II shows the case in which masking of the tinnitus percept increases linearly with level. In this case, the amount of fMRI activation is similar to normal at low stimulus levels (because there is little or no tinnitus masking). As the stimulus level (and hence the degree of tinnitus masking) increases, the line deviates increasingly from the no-tinnitus solid line. The deviation is because tinnitus-related activity is reduced during

stimulation increasingly as the degree of masking of the tinnitus percept increases with level. Curve III shows the case in which masking of the tinnitus percept increases in a non-linear fashion. Finally, curve IV shows the case in which tinnitus percept is not masked at any stimulus level. Since tinnitus-related activity is not reduced during the stimulated condition, fMRI activation is the same as in the subjects without tinnitus (see Figure 2a and c). Again, these presented cases show just a few possible outcomes that demonstrate our conceptualization and illustrate how heterogeneity in the tinnitus population can be taken into account. Correlating activation vs. level functions with independent measurements of tinnitus masking vs. level on a subject-by-subject basis will improve our ability to differentiate between the Saturation and the Physiological Masking models since predictions of the Physiological Masking model are dictated by the masking pattern. The next step in our studies is to obtain activation vs. level functions for lateralized tinnitus patients who have normal audiometry to further investigate relations between masking of the tinnitus percept and tinnitus-related abnormalities in the IC.

Activation vs. level in subjects without tinnitus: implications for tinnitus-related neural activity

The following is a demonstration of how level functions from subjects without tinnitus, combined with our present knowledge about tinnitus-related abnormalities in the IC lead to an intriguing deduction about underlying tinnitus pathophysiology. If abnormally low IC activation in lateralized tinnitus

subjects (star in Figure 5A) were a consequence of saturation (short-dashed line in Figure 5A), then saturation would start approximately at 45 dB SL according to our prediction in Figure 5. This is at least 30 dB below any saturation that might occur in subjects without tinnitus because our data shows no saturation for levels up to 75 dB SL. Since abnormally elevated neural activity (tinnitus-related activity) would presumably underlie this saturation, 30 dB (the minimum difference between saturation levels for subjects with and without tinnitus) would indicate the level of sound needed to elicit neural activity equivalent to the amount of tinnitus-related activity. 30 dB, however, is much greater than 13 dB SL, the maximum tinnitus loudness match for the tinnitus patients represented by the star in Figure 5A. Two possible explanations for this discrepancy are as follows. (1) the Saturation model may be correct, but the amount of tinnitus-related neural activity greatly exceeds what would be predicted from a loudness match. This would suggest that other influences such as affective or somatic factors [10] contribute to the amount of tinnitus-related neural activity. (2) The tinnitus-related abnormalities in the ICs [6] are not a consequence of saturation, but rather Physiological Masking.

Future directions

With our activation vs. level data from subjects without tinnitus, we are well positioned to obtain and interpret level functions in tinnitus subjects. Comparing these functions with independent measurements of tinnitus masking vs. level should help resolve the mechanisms underlying tinnitus-related fMRI abnormalities. By considering various forms of tinnitus, we may find that different mechanisms are at work in different tinnitus subpopulations. Even within the lateralized tinnitus population with normal audiometry, various fMRI activation abnormalities may become apparent as we expand our subject pool. If this were the case, the next step would be to determine whether the activation differences are correlated with particular tinnitus characteristics (e.g. etiology, level of distress, somatic modulation properties, etc.).

Conclusion

Our data demonstrating the dependence of IC activation on broadband noise level: (a) place constraints on the possible physiological mechanisms underlying tinnitus-related abnormalities seen with fMRI in lateralized tinnitus subjects; (b) leads

to predictions for activation vs. level functions in tinnitus subjects; and (c) lays a groundwork for testing these predictions and thus furthering our understanding of the pathophysiology underlying tinnitus.

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Neuroanatomical correlates of induced tinnitus

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Phantom auditory sensation tinnitus is often accompanied by severe annoyance and distress. Data from studies investigating the underlying patho-mechanisms of tinnitus indicate that severe tinnitus may have a central origin, or that aberrant signals from the periphery (tinnitus related neural activity) may be reinforced and further processing of signals facilitated by central centres mediating emotional control and memory. A few functional brain imaging studies addressed the cerebral mechanisms underlying the perception of tinnitus. These studies revealed variable activation. Besides the auditory cortices, one study implicated the hippocampus, another study a right hemisphere prefrontal and posterotemporal network in the perception of tinnitus, suggesting the involvement of emotional and attentional resources, respectively. The aim of the present study was to create a neuro-functional model of tinnitus. To imitate the auditory and emotional experiences associated with tinnitus in patients, we presented four aversive sounds to seven right-handed, healthy volunteers. Positron emission tomography (PET) was used to reveal the specific changes in cerebral activity. Five PET scans were obtained for each subject. Brain maps of subjects from scans with the induced tinnitus experience were contrasted to brain maps from a baseline condition in a subtraction procedure. Analysis of the preliminary data revealed activation in the primary auditory cortex, associative auditory areas, prefrontal areas, and the limbic system. The results show that processing of aversive auditory stimuli by healthy volunteers elicits activity in neural systems similar to those demonstrated in different PET studies on patients with tinnitus. The consistent activation of primary and associative auditory cortices and limbic system structures confirms that these centres subserve auditory and emotional processing of aversive sounds. The results give indirect evidence for the hypothesis that activation in prefrontal areas may be the underlying neurophysiological substrate of the continuous attention directed by subjects towards tinnitus, as suggested in an earlier PET study of tinnitus patients.

Introduction

Recent models of tinnitus suggest that auditory phantom perception may arise from any aberrant signal within the auditory system [1–3]. For all such signals, the models claim that conscious perception takes place in the cerebral cortex. However, few functional brain imaging studies have actually addressed the cerebral mechanisms underlying this perception [4–7]. To contrast conditions with and without tinnitus, most studies dealt with rare types of tinnitus (e.g., tinnitus changeable by oral-facial movement or eye gaze), or compared tinnitus patients with healthy volunteers. These studies attributed variable activation of the primary audi-

tory cortices [4,5], associative auditory cortices [5,6], and the left hippocampus [5] to the perception of tinnitus. Based on these heterogeneous results, explanations of the underlying mechanisms of tinnitus tend to differ. One 15-O-water PET-study found that tinnitus represents activity in an abnormal functional network between the primary auditory cortex and the limbic system, created by neural plasticity [5]. Another 15-O-water PET-study showed that a temporo-parietal auditory association area may underlie tinnitogenesis [6], whereas an FDG PET-study provided evidence of involvement solely of the primary auditory cortex [4]. In a recent 15-O-water PET-study [7] of tinnitus suppression by intravenous lidocaine or acoustic masking, the activity associated with the perception of tinnitus implicated a right prefrontal-temporal network in the process. Besides evidence of activation of associative auditory sensory regions, the results also suggested that cortical centres sub-

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erving attention and memory may underlie the continuous irritability associated with severe tinnitus.

The aim of the present study was to create a model of tinnitus perception by imitating the annoying and disturbing experience of tinnitus in normal volunteers by unpleasant auditory stimuli. Specific changes in neuronal activity were expected to be revealed by functional brain imaging with PET. Based on our earlier brain imaging studies [7,8] and theories of tinnitogenesis [1], we predicted that the perception of specific aversive auditory stimuli activates the auditory cortex, the emotion association centres of the limbic system, and the prefrontal lobes.

Methods

Activation mapping is based on the principle of relating changes in the regional cerebral blood flow (rCBF) to neuronal activity [9]. The localization of brain areas concerned with a specific mental task can be obtained by subtracting measurements of the rCBF during a "resting" condition and a state in which the brain is activated. Between these different conditions the global CBF is assumed to be unchanged [10]. Due to small changes in rCBF during such mental operations (changes approximately between 3 and 5%), the activation conditions have to be repeated in several subjects or within the same subject to enhance the signal-to-noise ratio.

Subjects

The study was approved by the local Research Ethics Committee and was conducted in accordance with the guidelines of the Declaration of Helsinki II. Seven right-handed, healthy volunteers (1 female, 6 males, aged 23–27 years, mean age 24.5 years) participated. Threshold audiometry and neurological examination revealed normal findings.

Acoustic stimulation

Ten subjects not involved in the PET study determined and selected the annoying stimuli (AS1 to AS4) from 20 different sounds by rating annoyance, dislike, nuisance, and disturbance caused by those sounds on a visual-analog-scale. The visual analogue scales consisted of 100 mm lines with endpoints denoted by the words "total absence" and "maximum" of annoyance, dislike, nuisance, and disturbance. The auditory stimuli were recorded on a digital audio tape-recorder Sony TCD-D7 and delivered binaurally through an audiometer Orbiter 922 using an EARtone 3A insert earphone. The auditory stimuli were as follows: (B1) baseline condition with no auditory stimulus, (AS1) continuous pure tone, 8 kHz, 85 dB SPL, (AS2) continuous pure tone, 8 kHz with a 30 Hz bandwidth, 85 dB SPL, (AS3) aversive sound generated by resampling (decreasing sampling frequency from 44.10 kHz to 22.05 kHz) an everyday sound-sample (scraping knife against plate), 85 dB SPL, and (AS4) the same sound as in AS3, but with 40 ran-

domly placed gaps of 20–50 ms duration. Tasks AS1–4 and B1 were counterbalanced within and across subjects.

Data acquisition and image analysis

Cerebral activation was measured as change in rCBF distribution as shown by the radioactivity in the brain after the intravenous injection of 15-O-labelled water, using an ECAT Exact HR47 PET-tomograph (Siemens/CTI). Tomograms were obtained in 3-D mode. For attenuation correction, a transmission scan was obtained in 2-D mode prior to emission scans. Emission scans were initiated at 60,000 true cps after bolus injection of 500 MBq 15-O-labelled water by counting in a single 40 s frame. Using filtered back projection, each PET volume was reconstructed after correction for attenuation and scatter to a 128 × 128 matrix of 2 × 2 mm pixels with a resulting resolution of 12 mm FWHM (Hann-filter, cut-off frequency of 0.15 cycles per second). The interval between successive injections was 12 min. Five emission scans were obtained. Auditory stimulations were initiated 10 s prior to injection and lasted throughout the scan. Subjects lay supine with the head fixed in a vacuum pillow. All scans were performed in a quiet darkened room with background noise only from the scanner (<20 dB SPL). To anatomically localize sites of increased rCBF, individual T1-weighted brain MR images were acquired prior to PET-scans on a Philips 1.5 T Gyroscan, with a Fast-Field-Echo sequence, 64 sagittal 2 mm slices, TE = 21.6 ms and TR = 41.7 ms. PET and MR images were individually co-registered to the Talairach and Tournoux co-ordinate system [11]. PET images were aligned to each other to compensate for any movement during the PET session.

Statistical analysis

The PET-volume obtained during the baseline condition was subtracted from PET-volumes obtained during each of the stimulated conditions (AS1 – B1, AS2 – B1, AS3 – B1, AS4 – B1), as well as from a pooled PET-volume of all stimulated conditions (ASavg – B1). The presence of significant focal changes in rCBF was tested by calculating the two-tailed *t*-statistic using a pooled standard deviation after pixel-by-pixel subtraction of PET-volumes using DOT [10]. By searching cerebral cortex (500 ml), *t*-values equal to or exceeding *t* = 4.3 were considered to represent significant (*P* < 0.05, corrected for multiple comparisons) focal changes in rCBF.

Results

Subtraction analysis revealed activation in the predicted regions, although without complete intertrial consistency. Results from the averaged tasks are presented in Table 1. Selected *t*-statistic maps are shown in Fig.1.

Table 1 Results of subtraction analysis of the averaged tasks versus baseline (ASavg – B1). Regional activations characterized by stereotaxic coordinates (x,y,z) and the corresponding Brodmann Area (BA).

| Anatomical localization | Right hemisphere | | | | | Left hemisphere | | | | |
|---|------------------|-----|-----|----|------|-----------------|-----|-----|----|-----|
| | Co-ordinates* | | | | | Co-ordinates* | | | | |
| | x | y | z | BA | t | x | y | z | BA | t |
| Transverse temporal gyrus (GT) | 39 | -25 | 9 | 41 | 11.0 | -44 | -26 | 5 | 41 | 7.3 |
| Superior temporal gyrus (GTs) | 60 | -31 | 11 | 22 | 5.5 | | | | | |
| Middle temporal gyrus (GTm) | | | | | | -68 | -10 | -15 | 21 | 3.9 |
| Superior frontal gyrus (GFs) | 17 | 48 | 41 | 8 | 37 | | | | | |
| | 20 | -13 | 54 | 6 | 3.7 | | | | | |
| Middle frontal gyrus (GFm) | 56 | 15 | 38 | 8 | 4.2 | | | | | |
| Inferior frontal gyrus (GF _i) | 51 | 15 | 26 | 44 | 3.8 | | | | | |
| | 60 | 29 | 8 | 45 | 3.7 | | | | | |
| Parahippocampal gyrus (Gh) | 16 | -2 | -15 | 34 | 5.8 | -21 | -1 | -30 | 28 | 4.7 |
| Amygdaloid body (NA) | 17 | -6 | -21 | - | 5.7 | -21 | -14 | -8 | - | 6.1 |
| Fusiform gyrus (GF) | 28 | -66 | -11 | 37 | 5.6 | | | | | |

* Talairach coordinates in mm: x (medial–lateral position relative to midline, right (+) / left (-)), y (anterior–posterior position relative to anterior commissure, anterior (+) / posterior (-)), and z (superior–inferior position relative to the intercommissural plane, superior (+) / inferior (-)).

Temporal lobe

All four auditory stimulation conditions activated the right primary auditory cortex (transverse temporal gyrus, Brodmann area [BA] 41), whereas the left side only was activated in AS3 – B1 and ASavg-B1. The associative auditory cortex in BA 22 + 42 was consistently activated bilaterally in AS2 – B1, AS3 – B1, and AS4 – B1, whereas averaging ASavg – B1 only revealed activation in the right hemisphere.

Frontal lobe

Prefrontal and frontal activations were predominantly seen in the right hemisphere in subtraction ASavg – B1 (superior, middle, and inferior frontal gyri, BA 6 + 8 + 44 + 45). In addition, AS2 – B1 and ASavg – B1 revealed left hemisphere activation in the inferior frontal gyrus (BA 44 + 45).

Limbic system

The parahippocampal gyrus (BA 28 + 34) and the amygdaloid body were activated bilaterally in ASavg – B1, whereas the individual subtraction analyses showed less consistent activation.

No activations were seen in anterior midline structures, such as the cingulate gyrus, or in the parietal lobe.

Discussion and Conclusion

The results from the present study indicate that the processing of aversive auditory stimuli activates the primary auditory cortex in both hemispheres, and engages a functionally linked network consisting of prefrontal regions and structures in the limbic system. The activation of the primary and associative

auditory regions is consistent with results from a large body of previous lesion and functional neuroimaging studies on processing of externally presented non-verbal auditory stimuli [12,13]. Similar auditory processing areas were activated during processing of internally generated sounds in functional brain imaging studies on tinnitus patients [4–7].

The activation of the limbic system (amygdaloid body and parahippocampal gyri) observed across the different conditions accords with results from studies on the functional neuroanatomy of negative emotional response to unpleasant stimuli [14–17]. The limbic system has also been implicated in processing auditory phantom perceptions [5]. A recent 15-O-water PET-study on tinnitus patients, who were able to change their tinnitus by oral-facial movements, revealed consistent activation of the limbic system (hippocampus) together with activation of the auditory cortex.

The parahippocampal gyrus has been associated with memory functions, whereas the amygdaloid body, which is closely connected to the parahippocampal gyrus, subserves emotion and has been implicated as a key structure in fear processing [18–22]. These limbic structures have in many studies on emotional processing been shown to cooperate with the orbitofrontal and ventromedial portions of the prefrontal cortex and the anterior cingulate gyrus [18,19,22–24]. The anterior cingulate gyrus has been hypothesized to play a role in mediating the attentional effects of affective arousal [21]. An involvement of these specific frontal regions in the perception of aversive sounds could not be substantiated in the present study. However, numerous activation and lesion studies have reported that the anterior cingulate gyrus together with the right dorsolateral prefrontal region subserves various attentional functions [e.g.: 25,26]. An activation of the

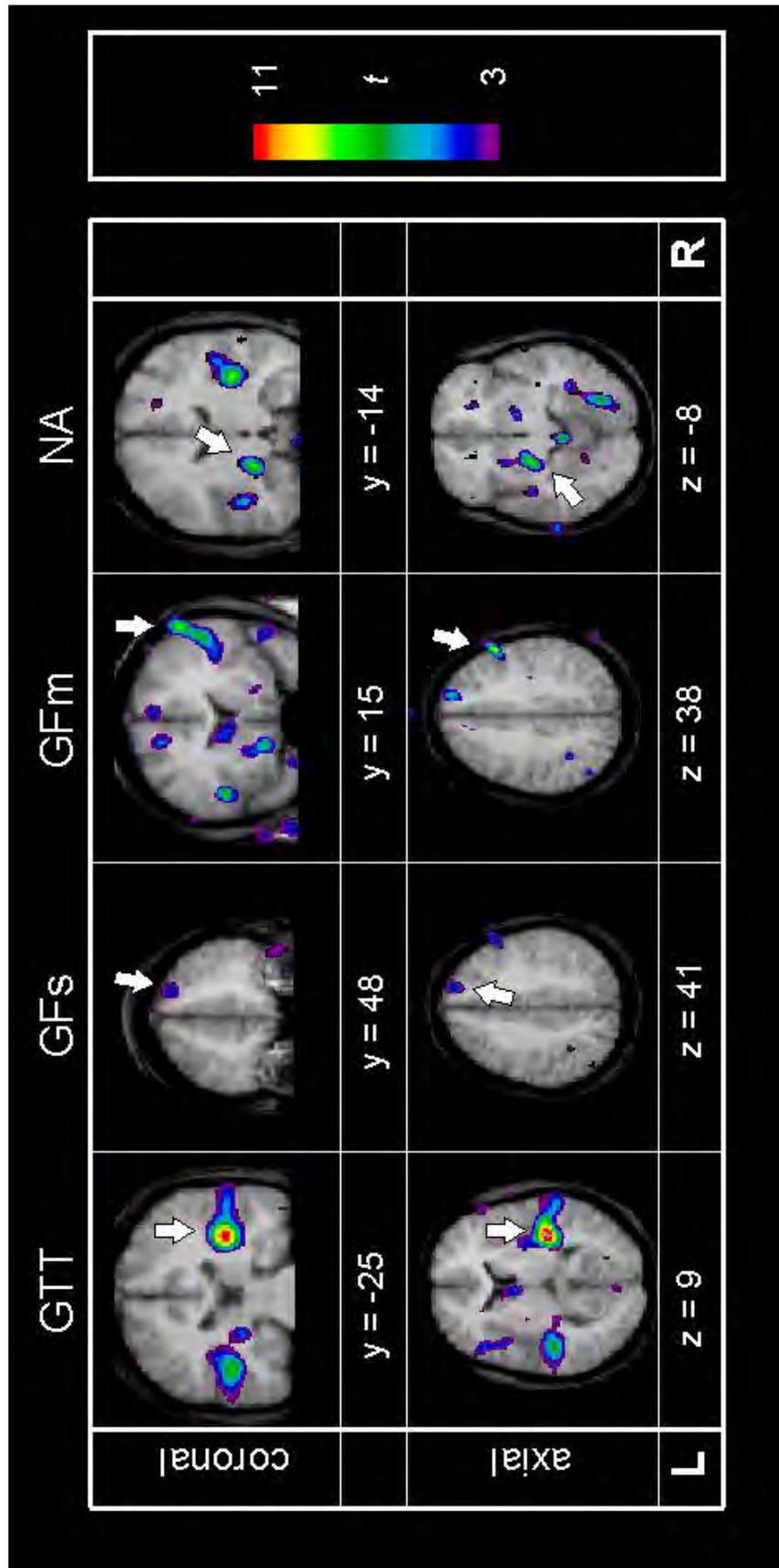


Figure 1 The t statistic map of the analysis of all test conditions (ASavg - B1) superimposed on coronal (upper row) and axial (lower row) slices of the average brain MR image of all 7 subjects. Selected peaks of activation corresponding to sites of activation given in Table 1 are indicated by white arrows. Dotted lines represent position of the intersectional plane between axial and coronal images. Coordinates (y and z) according to Talairach [11]. R: right, L: left. Other abbreviations: see Table 1.

dorsolateral prefrontal region was seen consistently throughout averaging conditions, ASavg – B1. Thus, even though the present study did not reveal an anterior cingulate gyrus involvement, the consistent dorsolateral prefrontal activation supports the notion that the perception and further processing of aversive auditory stimuli also involve specific attentional resources. The finding that negative emotional responses (amygdala) activate regions associated to both memory (parahippocampal gyrus) and attention (right prefrontal cortex) indicates that these processes may be interrelated [15].

The results may help to unveil the neuro-pathological mechanisms underlying tinnitus, because the perception of the unpleasant sounds in this study is psycho-acoustically similar to the perception of severe tinnitus. Indirectly this model provides further support for the hypothesis of tinnitus arising in functionally linked networks concerned with auditory processing, emotion, and attention [7]. Nevertheless, the heterogeneity of the results obtained in different functional brain imaging studies of tinnitus patients indicates that the imaging methods used at present may not be sensitive enough to reveal all facets of the brain activity subserving the sensation of tinnitus.

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Gaze-evoked tinnitus: A PET study

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The neural correlates of tinnitus perception were sought using positron emission tomography (PET) by taking advantage of four uncommon cases in whom this the sensation could be triggered by a deviation of horizontal gaze. This effect developed secondarily to surgical removal of a large tumor situated in cerebello-pontine angle.

By contrasting a condition where tinnitus is absent with a condition where the subject elicited his tinnitus, significant increases in regional cerebral blood flow were demonstrated bilaterally in the temporo-parietal (i.e. association) auditory cortices, but not in the primary auditory cortices. Individual results showed that whatever the side of the lesion (i.e. where the tinnitus is perceived), the cortical activation involved is clearly broader in the left hemisphere. The main two peaks of activation were located in the superior (BA 22) and medial (BA 21) temporal gyri. In the right hemisphere, the main peak of activation was centred in the posterior part of the temporal gyrus (BA 42) and extended dorsally towards the planum parietale (BA 40) and into the medial temporal gyrus (BA 21), where a second peak of activity was found. The location of the main peaks of activation in parieto-temporal regions is not surprising since the results from previous reports suggest that this area is dedicated to internally and externally generated sound representations and that (particularly on the left) this region is devoted to non-linguistic auditory tasks.

These results are in agreement with previous results suggesting that an auditory sensation can arise in the absence of activation in the primary cortex. Activation in association auditory cortex without activation of primary areas is compatible with reorganisation in subcortical structures leading to the activation of ascending auditory pathways projecting directly onto association cortices. Since activation of primary sensory cortices is the normal consequence of physical/external stimulation, it is tempting to conclude that subjective tinnitus arises from outside of the normal "chain of command". Nevertheless, the subjects readily assign qualities corresponding to frequency, intensity, and spatial localisation, perhaps a consequence of this subcortical organization.

Introduction

The mechanisms underlying tinnitus generation and perception remain poorly understood despite it is usually associated with peripheral disorders (hair cell damage responsible for clear or discrete hearing loss or very focused hearing losses due to spontaneous cochlear oscillations [1]). Tinnitus is generally thought as resulting from abnormal neuronal activity arising at any point along the auditory pathways which is interpreted as sound at a cortical

level [2,3]; like other phantom sensations such as phantom limb, it may also result from cerebral plasticity related to reorganisation following total or partial deafferentation. A major problem for identifying the neural correlates of tinnitus is the difficulty of controlling for the sensation. In order to contrast a reference condition with no phantom auditory sensation with an active condition during which tinnitus is heard, we took advantage of a rare form of tinnitus triggered by eye movements.

Methods

Subjects: A PET investigation was carried out in 4 right-handed gaze-evoked tinnitus patients (1 man aged 35 years and three women aged 45, 49 and 51

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years) who had developed a gaze-evoked tinnitus after resection of an acoustic neuroma of large size (>3cm) located in the cerebello-pontine angle. Patients gave their informed consent for the experiment which was approved by the local Ethics Committee. Prior to the operation the patients exhibited a unilateral profound hearing loss due to the compression of the acoustic nerve by the tumor, and they did not recover hearing after being operated. Each of them described a loud auditory sensation (generally matchable by a pure tone or a narrow band noise) felt in the deafferented ear (the right one for three of them) as soon as they move their eyes.

Preliminary study: It was determined that the tinnitus of these subjects behaved according to the point of the visual field towards which the patients' moved their eyes. The patients were asked to pursue a light moving from a fixed central reference, eliciting no sensation, towards the periphery; this test was performed using the Goldman apparatus. The sensations elicited by eye movements towards 168 different points of the visual field were matched in bandwidth, frequency and intensity with external sounds delivered contralateral to ear with which the tinnitus was associated, namely the intact ear by means of a Madsen OB-822 audiometer with a TDH 39P earphone. For each discrete sensation matched, the equivalent hearing level was measured. Thus, accurate frequency and intensity maps were constructed for each patient. These maps were used to define the eye movement the subjects had to achieve in the different tasks performed during the PET study.

PET study: Regional cerebral blood flow (rCBF) was assessed by recording cerebral radioactivity following the i.v. injection of $H_2^{15}O$. Each subject received 12 injections of 9mCi: six scans during reference task consisting in vertical eye movements evoking no tinnitus and six scans during active task i.e. horizontal eye movements eliciting the loudest tinnitus. Reference and active tasks were similar, the only differences between them were the absence or presence of tinnitus and the direction of eye movements (vertical versus horizontal). Eye movements started 10 s prior to the PET data acquisition. PET images were acquired parallel to the bicommissural (AC-PC) plane using a Siemens CTI HR + camera. Sixty eye movements, between two light emitting diodes, alternately lighting through a black background, were performed during one scan (60s). Standardised procedures of realignment, normalisation, smoothing and statistical analysis were performed using SPM 97d.

Results

Tinnitus frequency and intensity maps

Exploring patients' visual field allowed us to derive tinnitus frequency and intensity maps for each of the four patients. An example is provided in Figure 1. Some observations were consistent among the

maps obtained from the four subjects: (i) the tinnitus varied in frequency according to the hemifield explored; (ii) subjective intensity increased with eye gaze deviation, the loudest tinnitus being elicited by eye movement in the horizontal plane, an effect consistent among subjects; (iii) there is a space region, (found in the azimuth (also consistent among subjects) towards which eye movements did not elicit any sensation. When elicited, the sensation rapidly decreased as soon as the target is reached and eye movement stopped.

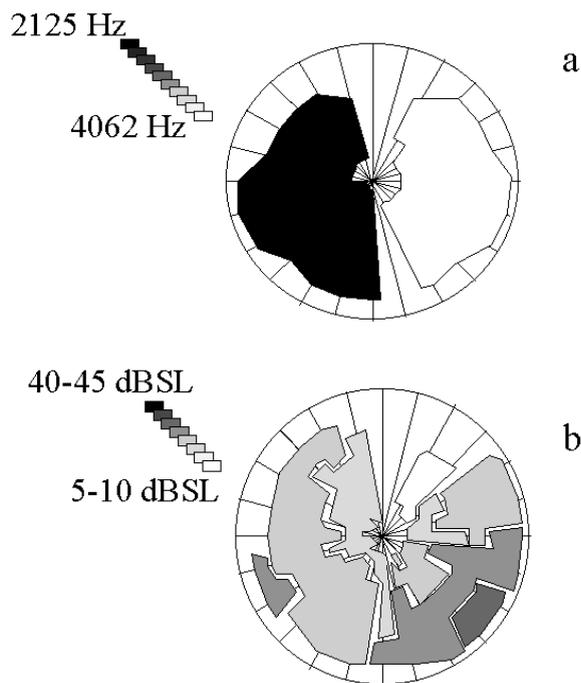


Figure 1 Frequency (a) and intensity (b) maps built from the exploration of the visual field of a patient whose right ear is deafferented. Note that (1) tinnitus frequency varied according to the hemifield and (2) that tinnitus subjective intensity increased with eye gaze deviation.

This fact explains that during PET scanning, it was necessary to repeat the eye movement for inducing a sustained tinnitus. The lights were therefore switched on and off at a rate of 1/s (2s for forwards + backwards).

PET study

The use of an eye movement task in the reference condition resulted in subtracting the activity linked to visual and oculomotor processes. Indeed observations were made as well in a normal control subject without tinnitus, in whom the reference condition was fixation on the central light-emitting diode and the active condition was an horizontal eye movement. This results clearly revealed the structures normally involved in the oculomotor task.

When tinnitus and no tinnitus conditions were contrasted, a slight rCBF increase appeared in

Table 1 rCBF increase associated with phantom auditory sensation (4 subjects)

| Subtraction | Side | Anatomical Region | Brodmann Area | Coordinates | | | ρ (Z score) |
|-----------------|------|-----------------------|---------------|-------------|-----|-----|------------------|
| | | | | x | y | z | |
| HEM tinnitus | R | Superior temporal | 42/22 | 62 | -34 | 22 | 0.015 (5.34) |
| Minus | R | Medial temporal | 21 | 54 | -46 | 0 | 0.015 (3.53) |
| VEM no tinnitus | R | Horizontal eye muscle | | 24 | 28 | -34 | 0.020 (5.22) |
| | L | Superior temporal | 22 | -70 | -42 | 22 | 0.024 (4.79) |
| | L | Medial temporal | 21 | -68 | -58 | 6 | 0.024 (4.48) |
| | L | Occipito-parietal | 7 | 0 | -92 | 44 | 0.223 (3.95) |
| VEM no tinnitus | R | Vertical eye muscle | | 26 | 40 | -29 | 0.000 (7.38) |
| Minus | L | Vertical eye muscle | | -26 | 42 | -22 | 0.000 (6.60) |
| HEM tinnitus | R | Superior frontal | 8 | 22 | 24 | 54 | 0.034 (4.61) |

VEM: vertical eye movements; HEM: horizontal eye movements. R and L indicate left or right hemisphere. Statistics have been corrected for multiple comparisons.

patients in a region of the parieto-occipital gyrus (belonging to Ba 7) and in regions associated with horizontal eye muscles during active task implying an horizontal eye movement compared with the vertical eye task. When reverse comparison was done, regions associated with vertical eye muscles as well as the superior frontal gyrus (frontal eye field) were activated. Differences in the muscles involved in horizontal and vertical eye movements and in the motor command for each kind of movements account for these activations. Parieto-occipital gyrus is known to be involved in visuo-spatial processing, particularly in the analysis of visual features in order to perform a movement [4]. This region is presumably active in both the reference and active conditions given that patients performed an oculomotor task requiring analysis of the visual field. The fact that rCBF in the occipito-parietal gyrus was greater in the active condition could simply be a consequence of differences in the location of the visual target respectively in the reference and the active conditions. The location of the occipito-parietal activation within the left hemisphere is consistent with a greater specialization of the latter in the processing of spatial relationships among objects [5], processing which is implicitly included in our task.

The most interesting finding consists of a bilateral rCBF increase in temporo-parietal regions concomitant to tinnitus perception which was revealed by a group-data analysis. Although bilateral, the activation is more extensive but weaker in the left hemisphere whatever the side of the surgically treated ear. In the right hemisphere two peaks of activation were observed. The main one was centred in the posterior part of the superior temporal gyrus, at the junction between the planum temporale and the planum parietale (BA 42, 22 and 40). Referring to accurate topographical maps [6], this region is most likely located in the secondary auditory cortex (BA 42) and not in the primary auditory cortex. A second peak was found in medial temporal gyrus (BA 21). In the left hemisphere, two main peaks of activation were found respectively in the superior temporal gyrus (BA 22) and in the medial temporal gyrus (BA 21). The activation largely spreads out from one peak to the other and around the first peak towards the inferior parietal lobule (BA 40). Activation in the superior temporal

gyrus (BA 42/22) and the medial temporal gyrus was a pattern common to both hemispheres.

Discussion and conclusion

The parieto-temporal location of the activation can be explained readily. Parieto-temporal regions located at the junction between BA 22 and 40 have been found to be involved in both song imagery and song perception [7] implying that this region is responsive to either internally or externally generated representations. More anterior regions, closer to the primary auditory cortex (BA 42) have been shown to be active in perceptual tasks only. Therefore, Zatorre *et al.* [7] proposed that primary auditory cortices are essentially devoted to the extraction of stimulus features from the environment. In contrast, secondary auditory regions are suggested to be specialized for high-order processing including the internal representation of auditory stimuli. Activations in a posterior temporal region during tinnitus perception is in complete agreement with this hypothesis.

In their song imagery task, Zatorre *et al.* [7], found an equal activation of each of the the bilateral parieto-temporal regions. They proposed that the right hemisphere activation accounts essentially for musical representations while the left reflects vocal representations. The right hemisphere is known to be predominantly involved in musical perceptual tasks and right hemispheric dominance is evident for basic judgments about pitch [8]. In our study sample, the parieto-temporal region was activated on both sides with a higher Z score for the right hemisphere, compatible with the non-verbal content for the perception of tinnitus. In a case of musical hallucinosis, an activation of the right posterior middle temporal gyrus was found [9]. The second peak of our right hemispheric focus is located exactly at the same place, in the middle temporal gyrus. Such an activation is consistent with the fact that patients identify their sensation as 'their' highest or lowest sound, by comparison with the pitch stored in memory, corresponding to what they 'hear' when they move their gaze in the opposite direction (see Figure 1). This also agrees with the suggestion by Fiez *et al.* [10] that this region

could be involved in acoustic analysis and short-term store of acoustic information, and particularly in the right hemisphere [9]. Although activated in auditory [11] and non-auditory verbal tasks [12] as well, the parieto-temporal auditory region (particularly left) was demonstrated to be preferentially involved in non linguistic auditory tasks, when compared to speech tasks [12].

The most important finding of this study is the absence of activation within the primary auditory cortex. This observation is in disagreement with those of two PET studies conducted on patients suffering from long-standing tinnitus. Arnold *et al.* [12] reported an increase in metabolic activity of the left primary auditory cortex in a group of sufferers using PET with F-deoxyglucose and more recently, Lockwood *et al.* [13] showed variations in levels of rCBF in the primary auditory cortex that correlate with tinnitus loudness in tinnitus patients able to modulate the loudness of their tinnitus. The absence of activation of primary auditory regions together with an activation of auditory association areas in gaze-evoked tinnitus could be interpreted two ways. First, the activation does not correspond to the processing of a signal coming from subcortical auditory structures, and the parieto-temporal activation reflects the site of tinnitus generation. Second, some subcortical ascending auditory pathways projecting to association areas and not to primary cortex are activated by eye movements. From the first interpretation, tinnitus would be the result of the cortical reorganisation following the deafferentation and reattribution of the substrate representing the deafferented structures to the neighbouring body parts. Such an explanation is commonly admitted for phantom limb sensation [14]. In gaze-evoked tinnitus, reorganisation should occur between deafferented auditory areas and areas involved in the control of eye movement. Such a reorganisation is unexpected. The parietal component of cortical areas involved in volitional and visually guided saccades [15] is indeed not adjacent to auditory areas (anatomical proximity being necessary, presumably, to allow reorganisation), and do not overlap the areas activated in the current study. Moreover, gaze-evoked tinnitus occurs even when eyelids are closed, indicating that tinnitus can also be elicited by spontaneous eye movements; that precludes the cerebral cortex which is only involved in reflexive and volitional saccades [16] and imply the involvement of subcortical pathways. This suggests that the cross-modality interference from which the tinnitus results does not take place in the cortex but rather in subcortical structures. The activity observed in temporo-parietal regions is therefore more likely to reflect the processing of an ascending neural signal as proposed in the second hypothesis.

The idea that the neural signal substrate of tinnitus must develop from subcortical structures is supported by clinical observations. Central lesions virtually never induce sensations like tinnitus and phantom-limb, and people with congenital sensory deprivation do not usually experience such sensa-

tions. This suggests that deafferentation in itself is not sufficient to explain these sensations, but that the ability of sensory systems to generate and transmit aberrant neural signals is necessary. These sensations therefore have been attributed to the cortical processing of neural signal arising from subcortical structures, perhaps originating in damaged primary nerve endings (see [17] for review).

Direct activation of auditory association areas by ascending signals without activation in the primary cortex, however, is both anatomically and physiologically plausible. Auditory association areas have been shown to remain functional after lesions of the primary cortex [18] and temporo-parietal regions, are directly responsive to acoustic stimuli [19]. It is now admitted that the central auditory system, like the visual system, is divided into two parallel streams [20]. One is preferentially involved in the representation of space, involving parietal regions which are activated in our study. Activation in these regions without activation in more dorsal and anterior regions is therefore compatible with the processing of a signal emerging from auditory subcortical relays and also suggests that spatial aspects of gaze-evoked tinnitus are possibly more important than aspects related to the identification of the phantom sound.

Silbersweig *et al.* [21] and Griffith *et al.* [22] previously reported activations in BA 21 and 22 (auditory association areas) without activation in primary auditory region in patients experiencing hallucinations either transient verbal and auditory [21] or musical [22]. Our present finding confirms that the activation of primary auditory regions is not necessary for conscious auditory perception and that the main contribution to the perception of tinnitus comes from association auditory areas. Gaze-evoked tinnitus is very unlikely to result from cortical reorganisation only. Activity in association auditory areas without activation of primary regions is compatible with reorganisation in subcortical structures leading to the activation of ascending auditory pathways which directly project onto association areas. The activation of temporo-parietal association areas certainly reflects the integration of a large number of perceptual qualities of tinnitus like frequency, intensity and spatial localisation. It also probably accounts for some cognitive processing of tinnitus achieved by patient such as mental manipulation of pitch (judgement, retention and comparison).

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Tinnitus effects on ABR thresholds, waves and interpeak latencies

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Objectives: Tinnitus seems to result from an aberrant neuronal activity within the auditory pathways, misinterpreted as a sound sensation by the auditory centers. Using pure-tone audiometry (PTA), some authors demonstrated the influence of tinnitus on the hearing perception. Regarding the auditory brainstem responses (ABR), its influence was very heterogeneous, varying from a simple interference in trace morphology to significant alterations in the latencies of the waves and/or interpeak intervals.

Methods: In order to clarify the possible influence of tinnitus on the auditory brainstem responses, 108 ears from 54 patients were evaluated, being composed of 27 with and 27 without tinnitus. Patients with intermittent tinnitus, conductive or profound sensorineural hearing loss and retro-cochlear disease were excluded. Each one underwent PTA and ABR at the same day. Assuming that the best correlation of the click stimulus in ABR occurs with the pure-tone average in 2 and 4 kHz, all ears were divided according to the average of PTA thresholds in 2 and 4 kHz in: up to 20 dBHL (T1, with tinnitus, and C1, without tinnitus) and higher than 20 dBHL (T2, with tinnitus, and C2, without tinnitus), thus comprising 4 groups, 2 with and 2 without tinnitus. Analysis of parameters was always done between one tinnitus group and its matched control group, verifying the correlation between PTA and ABR thresholds, as well as the latency of waves I, II, III, IV, V and interpeak intervals I-III, III-V and I-V.

Results: In ears with average of PTA thresholds up to 20 dBHL, there was a significant increase of ABR threshold and latency of waves I and II in T1, when compared to the control group (C1), what didn't happen in groups with average of PTA thresholds higher than 20 dBHL. The latency of waves III, IV, V and interpeak intervals I-III, III-V and I-V didn't show any difference between tinnitus and control ears, independently of pure-tone thresholds.

Conclusions: Our findings support the influence of tinnitus in the electrical activity of auditory pathways. As the results were significant only between the groups with normal hearing sensitivity, the changes provoked by hearing loss seem to avoid the evaluation of tinnitus effects, at least in the present methodology.

Introduction

Tinnitus is considered an auditory illusion or an endogenous sound sensation, that is, any sound perceived by the patient without an external sound source [1,2,3,4,5].

As a complaint, it dates back to ancient times. Historical data show that the Ebers papyrus, from XVI BC century [6,7], is the oldest document to mention tinnitus, proposing a treatment for the "bewitched ear" with infusion of oils in the external auditory canal. Among the Assyrians (700 BC), drugs as opium, belladonna and *cannabis* were routinely used. At that time, magical connotations led

to the faith that "if the hand of a ghost seizes a man, his ears sing . . ." [7]. In the Middle Age, tinnitus treatment began to be specific for each case, depending on the presence of other symptoms. In 1821, Itard was the first to dedicate a whole chapter to tinnitus in his "Traité des Maladies de l'Oreille et de l'Audition" [8].

Tinnitus seems to result from an aberrant neuronal activity within the auditory pathways, misinterpreted as a sound sensation by the auditory centers. Clinically, it has an important association with hearing loss in 85 to 96% of the cases, showing a close association between both symptoms [2,9,10,11,12]. Using pure-tone audiometry (PTA), some authors demonstrated the influence of tinnitus on the hearing perception. Regarding the auditory brainstem responses (ABR), some changes have already been attributed to tinnitus, but its influence was quite heterogeneous, varying from a

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simple interference of the tracing⁴⁹ to significant alterations in the latency of one or more waves [13,14,15] and/or interpeak intervals [14,16]. Would tinnitus affect the electrical activity of the auditory pathways? If so, might tinnitus effects be noticed on the auditory brainstem responses?

The objective of the study was to evaluate the possible influence of tinnitus on ABR, comparing ears with and without tinnitus regarding the latency of the waves I, II, III, IV, V and of the interpeak intervals I-III, III-V and I-V.

Methods

We prospectively studied 108 ears from 54 patients from February to June 1997. There were 27 tinnitus patients sequentially seen in the Otolaryngology Department of University of São Paulo Medical School (Group T – tinnitus) and 27 volunteers without tinnitus (Group C – control). The ages ranged from 25 to 78 (average = 48,85; standard deviation = 11,24). There were 45 white and 9 black patients; as to sex, 7 were male and 47 female patients.

Each patient underwent pure-tone audiometry (PTA) and auditory brainstem responses (ABR) at the same day. Groups T and C were subdivided in 2 groups each, according to the pure-tone average at 2 and 4 kHz. When that average was up to 20 dB HL, the ears were grouped in the subdivisions T1 (with tinnitus) or C1 (without tinnitus). When average was higher than 20 dB HL, the ears were grouped in the subdivisions T2 (with tinnitus) or C2 (without tinnitus). Groups T1 and C1 were kept homogeneous in relation to sex and age, as well as groups T2 and C2.

In order to match the groups as much as possible, patients with conductive or mixed hearing loss, profound sensorineural hearing loss or known retrocochlear disease were excluded.

Summarizing, the patient selection was as follows:

Tinnitus Group (T): composed by 27 individuals with constant and unilateral (18) or bilateral (9) tinnitus for at least 3 months, totaling 36 ears with tinnitus. Subdivisions:

- (a) T1: pure-tone average at 2 and 4 kHz \leq 20 dB HL (16 ears);
- (b) T2: pure-tone average at 2 and 4 kHz $>$ 20 dB HL (20 ears).

Control Group (C): composed by 27 volunteers without tinnitus, carefully chosen to match sex and age in both groups. Besides their 54 ears without tinnitus, the Control Group included the remaining 18 ears without tinnitus from patients with unilateral tinnitus, totaling 72 ears. Subdivisions:

- (a) C1: pure-tone average at 2 and 4 kHz \leq 20 dB HL (39 ears);
- (b) C2: pure-tone average at 2 and 4 kHz $>$ 20 dB HL (33 ears).

The same audiologist performed all PTA exams

in an audiometric cabin using the Madsen OB70 audiometer with original phones. The frequencies tested were 0.25, 0.5, 1, 2, 4 and 6 kHz.

The ABR exams were performed using the Amplaid MK 12 system with the following technical specifications: amplification 5 μ V, low-pass and high-pass filters of 100 and 2500 Hz, time of analysis of 10 ms, rate of stimuli of 21 clicks/s, alternate polarity, duration of 100 μ s, intensity from 10 to 130 dB peSPL and sum of responses at 2000 stimuli. The initial stimulus was always a 110 dB peSPL click, applied to a TDH 49 transducer. According to the morphology of the answer, its intensity was decreased by 10 or 20 dB peSPL steps until determining the ABR threshold. Whenever possible, the latencies of all waves were determined in each intensity and, when doubtful, were not considered for analysis.

The following parameters were studied, always comparing the ears of study groups with those of each matched control group (T1-C1 and T2-C2):

- (a) latency of waves I, II, III, IV and V;
- (b) latency of interpeak intervals I-III, III-V and I-V.

For statistical purposes, the parametric test "Differences between Averages" was applied for analyzing the latency of the waves and interpeak intervals, once they are samples with a normal distribution. The significance level adopted was 5% ($p = 0.05$), as recommended for biological tests.

Results

Comparing the groups with average of PTA thresholds up to 20 dB (T1 and C1):

- there was a significant increase of the average of the latency of waves I ($p = 0,0028$; Figure 1) and II ($p = 0,0487$; Figure 2) in T1 (with tinnitus) when compared to C1 (without tinnitus).

- there was no difference between the average of the latency of the waves III, IV, V (Figure 3) nor of the interpeak intervals I-III, III-V and I-V (Figure 4).

On the other hand, comparing the groups with average PTA threshold higher than 20 dB (T2 and C2):

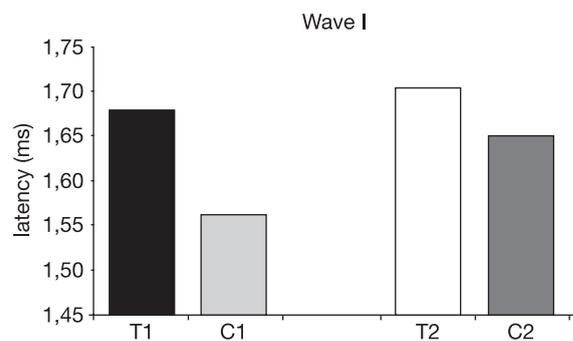


Figure 1 Average of the latency of the Wave I in the study groups and matched control groups

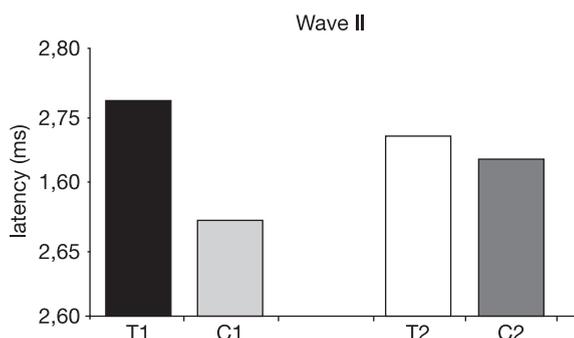


Figure 2 Average of the latency of the Wave II in the study groups and matched control groups

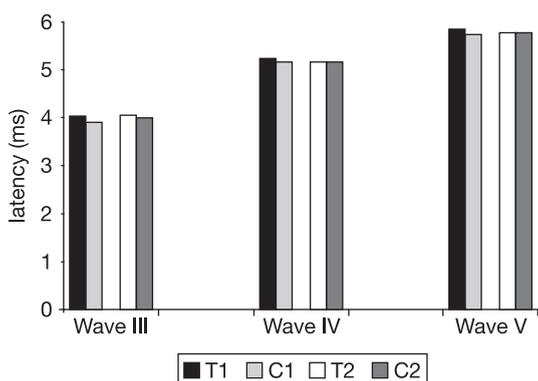


Figure 3 Average of the latencies of the Waves III, IV and V in the study groups and matched control groups

– there was no difference between the average of the latencies of the waves I, II, III, IV, V (Figures 1, 2 and 3) nor of the interpeak intervals I–III, III–V and I–V (Figure 4).

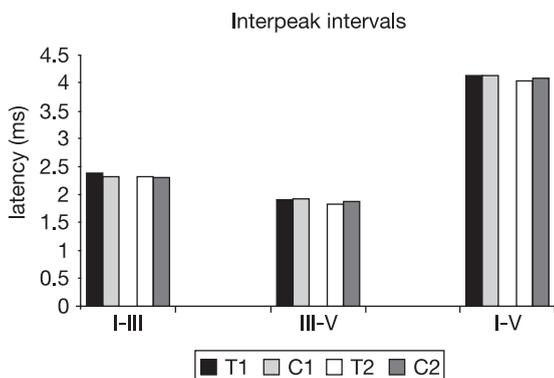


Figure 4 Average of the latencies of the interpeak intervals I–III, III–V, I–V in study groups and matched control groups

Discussion and Conclusions

The possibility of objectively measuring the presence of tinnitus would be very useful. This would allow the location of its generating site, the evaluation of the effectiveness of a certain treatment, or still, its confirmation or exclusion in cases of judicial litigation. Unfortunately, no such test was capable

of identifying or predicting the presence of the tinnitus until now [17].

ABR analyses the processing of signals as far as brainstem level. Some studies related the waves I, II, III, IV and V, respectively to the cochlear nerve, cochlear nuclei, superior olivary complex, lateral lemniscus and inferior colliculus [18]. More recently, the possibility of measuring the action potential of each structure intra-operatively allowed advances in identifying neural generators of each wave. Moller demonstrated in several studies that wave I is generated by the most distal portion of the cochlear nerve and wave II, by its proximal portion, closer to the brainstem [15,19,20,21]. Scherg; von Cramon also agreed and stated that generation of waves III, IV and V have the participation of more than one anatomical structure for each wave [22]. Thus, wave III seems to be generated mainly by ipsilateral cochlear nucleus, possibly receiving contributions of the ipsilateral superior olivary complex. The wave IV remains obscure even after intra-operative recording, being possibly generated by the own superior olivary complex. Finally, wave V originates from the contralateral lateral lemniscus, close to the inferior colliculus [23].

Despite the controversy in literature about the several aspects of tinnitus, there is consensus concerning an aberrant electrical activity in the auditory pathways in tinnitus patients [3,5,24,25]. Therefore, this abnormal and constant electrical activity in the auditory pathways should interfere in the registration of ABR, possibly for changing its synchronism, since the electrical response evoked by the click needs to travel by the same pathways occupied by the constant activity of tinnitus.

The diversity of findings in ABR of tinnitus patients is large, such as: interference in morphology of tracing and increase of transmission time in brainstem [26], increase in latency of wave I [13,14,27]; decrease in interpeak interval I–III [14]; alteration of wave V [3,15], increase of interpeak intervals I–III, III–V and I–V, also in the contralateral ear [16]. Conversely, other studies did not demonstrate any difference in individuals with and without tinnitus [10,28,29].

Our study revealed a significant increase of the latencies of the waves I and II in T1 in relation to C1 (Graphs 4a and 4b). Our findings agree with Maurizi and Ikner; Hassen with respect to wave I, although we have also identified increase in latency of wave II, not described previously. If we consider that both waves represent different portions of the cochlear nerve [21], these findings are in agreement with Jastreboff's neurophysiological model which assumes that tinnitus generation occurs in the periphery of auditory pathways [3]. Therefore, in ears with tinnitus and pure-tone average up to 20 dB HL, ABR allows some association with its physiopathology.

Tinnitus is a symptom associated with countless aetiologies. The fact that we studied a sample of patients results in the heterogeneity of diagnoses, which perhaps can justify such varied results in

literature, sometimes even opposed to each other, as the one of Maurizi and Bergman; Bertora. It is natural to think that the results of each study can just reflect the aetiology which is more common in a specific group, and that the several authors may have studied representative groups of different aetiologies. Perhaps future studies in tinnitus patients with similar aetiology can clarify these doubts. Another plausible explanation for those differences is that some studies compared different populations of tinnitus and non-tinnitus patients [3,10,13,28,29], while others compared findings in the same patient before and after abolition of the symptom, or among ears with and without tinnitus [14,16,26,30].

What is the effectiveness of ABR for differential diagnosis of tinnitus? Dickter noticed the diversity of discoveries in patients with tinnitus and similar audiometries, reinforcing that one should not compare its usefulness to the detection of VIII nerve tumours [31]. On the other hand, Shulman et al. consider it a good sensitive method to detect suggestive alterations caused by tinnitus, advising its routine accomplishment in these patients [4,26,32]. For Jastreboff, its usefulness is limited to the possibility of identifying the generating sites of tinnitus starting from analysis of the inferior auditory pathways [3].

Through our methodology, we believe that ABR was capable of showing specific alterations of tinnitus in waves I and II in the ears of T1. This means that, in individuals with pure-tone average at 2 and 4 kHz up to 20 dB HL, this exam can help to confirm a peripheral aetiology, but cannot be transposed to patients with sensorineural hearing loss. Perhaps, with the absence of difference between T2 and C2, the use of this exam should be restricted to the exclusion of retrocochlear lesions in patients with sensorineural hearing loss.

Our findings, as well as literature, suggest that the analysis of the restricted and minority group of patients with tinnitus and auditory thresholds within normal limits may be the key for understanding the mysteries that involve tinnitus. We say this because the changes provoked by the concomitant hearing loss seem to hinder the onset of possible tinnitus effects, at least in the employed methodology.

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Input/output function of late auditory evoked potentials (LAEPs) and objectification of tinnitus ear in unilateral tinnitus sufferers

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The objective of this study was to objectify the affected ear by tinnitus in unilateral tinnitus subjects. Late auditory evoked responses were recorded from Fz in response to 1000 Hz tone bursts of various intensities in 9 unilateral tinnitus sufferers. N1/P2 component amplitude and N1 and P2 latencies were measured. Objective identification of the affected ear in unilateral tinnitus sufferers was found feasible on the basis of N1/P2 intensity-dependence and N1-P2 amplitude.

Introduction

Tinnitus, as a phantom auditory perception, is basically subjective, but some objective method would be useful to detect and evaluate it in humans. First, this would allow confirmation of the symptom (just as the audiogram is useful to confirm and quantify hearing loss). Second, it might help shed light on the underlying mechanisms of tinnitus if, for example, correlations emerged with electrophysiological parameters.

Hoke *et al.* [1,2] suggested differences in auditory evoked magnetic fields between tinnitus patients and controls, namely with regard to the M100 and M200 waves. Other reports, however, failed to support the notion of tinnitus-specific abnormalities in auditory-evoked magnetic fields [3,4].

In our study, we hypothesized differences in cortical auditory information processing between tinnitus ear and non-tinnitus ear in unilateral tinnitus subjects; our objective was to objectify change in auditory treatment associated with the presence of tinnitus by electrophysiological method. We choose LAEPs technique using various intensities of stimulation (60 dB SPL, 70 dB SPL, 80 dB SPL and 90 dB SPL) because large interindividual responses have been described with increasing stimulus intensity, particularly the N1-P2 component: in some individuals, N1-P2 amplitude increases with stimulus intensity, while in others a gradual increase at

low stimulus intensities and constant or even decreasing amplitude at the higher-tested intensities were found [5,6,7]. A similar intensity-dependence had also been described in visual modality and this phenomenon is generally described to reflect an overall mechanism implicated in sensory treatment [8,9]. Several authors [8,9] have suggested this intensity-dependence relates to central factors protecting the cortex against overstimulation.

Then, if tinnitus modify auditory treatment in one ear, we expected to objectify this change via intensity-dependence of N1-P2 component compared to the other ear. Responses were derived from the Fz site because the cortico-subcortical loop regulating auditory stimulus intensity control (as evidenced by the intensity-dependence phenomenon) might include frontal cortex participation [5].

Methods

Nine adults with unilateral tinnitus (7 males and 2 females), 7 had right sided tinnitus and 2 had left sided tinnitus, were tested. All subjects underwent audiometry, tympanometry and stapedial reflex testing, and those with hearing less than 20 dB HL at 1 kHz in one or both ears were excluded, as were those with suspected middle ear disease.

Auditory evoked potentials were elicited by a sequence of 40 tone bursts of 1000 Hz (200 ms duration, 20 ms rise and fall time) at a repetition rate of 0.9/sec, presented monaurally through headphones. To minimize contamination of the evoked potentials by EEG alpha rhythm, subjects

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kept their eyes open, focusing on a set point. Three separate averages were taken per intensity, each subject undergoing the same sequence: 70–80–60–90/80–90–70–60/70–60–80–90 dB SPL. Each intensity was presented successively to the left and the right ear. The mean of the three averages was taken as the final measured value for each subject.

LAERs averages were obtained by a Nicolet Pathfinder II. Responses were derived from Fz referred to linked earlobe electrodes (A1 and A2) with the reference always ipsilateral to stimulation. Electrode sites were cleaned with abrasion to keep resistance below 5 kohms. The recorded activity was filtered with a 1–30 Hz bandpass (Butterworth filter, roll off of 12 dB/octave) and the sample rate was of 1280 samples/second.

N1 and P2 latencies and N1-P2 amplitude were measured after 2–20 Hz digital filtering. The intensity effect for N1-P2 amplitude, N1 and P2 latencies, for each ear, was tested by Friedman non parametric analysis of variance; if the Friedman-test showed a significant intensity effect, then the Wilcoxon-test was used to probe specific differences among stimulus intensities. To compare the affected ears and the non-affected ears of the unilateral tinnitus sufferers (paired measures), we also used the Wilcoxon-test. Differences were considered significant when $p \leq 0.05$.

Results

The grand average of auditory evoked potentials, obtained at 90 dB SPL, for ears affected by tinnitus and responses for the contralateral ears are shown in Figure 1.

Neither N1 latency nor P2 latency were different between the tinnitus ears and the non-tinnitus ears. N1-P2 amplitude varied significantly with stimulus intensity in the affected ear of tinnitus subjects. However, the effect of intensity proved non-significant in the unaffected ears. Figure 2 shows the mean amplitude of N1-P2 component at the various stimulus intensities in tinnitus ears and non-tinnitus ears. The Wilcoxon test reveals significant differences between the tinnitus ears and the non-tinnitus ears at 80 dB SPL and 90 dB SPL.

Discussion-conclusion

Objective identification of the affected ears in unilateral tinnitus sufferers was found feasible on the basis of an increase of N1-P2 intensity-dependence and N1-P2 amplitude. Unfortunately, the identification of individual tinnitus ears was not possible on all the subjects. Responses for the tinnitus ear differed significantly from the contralateral ear only in

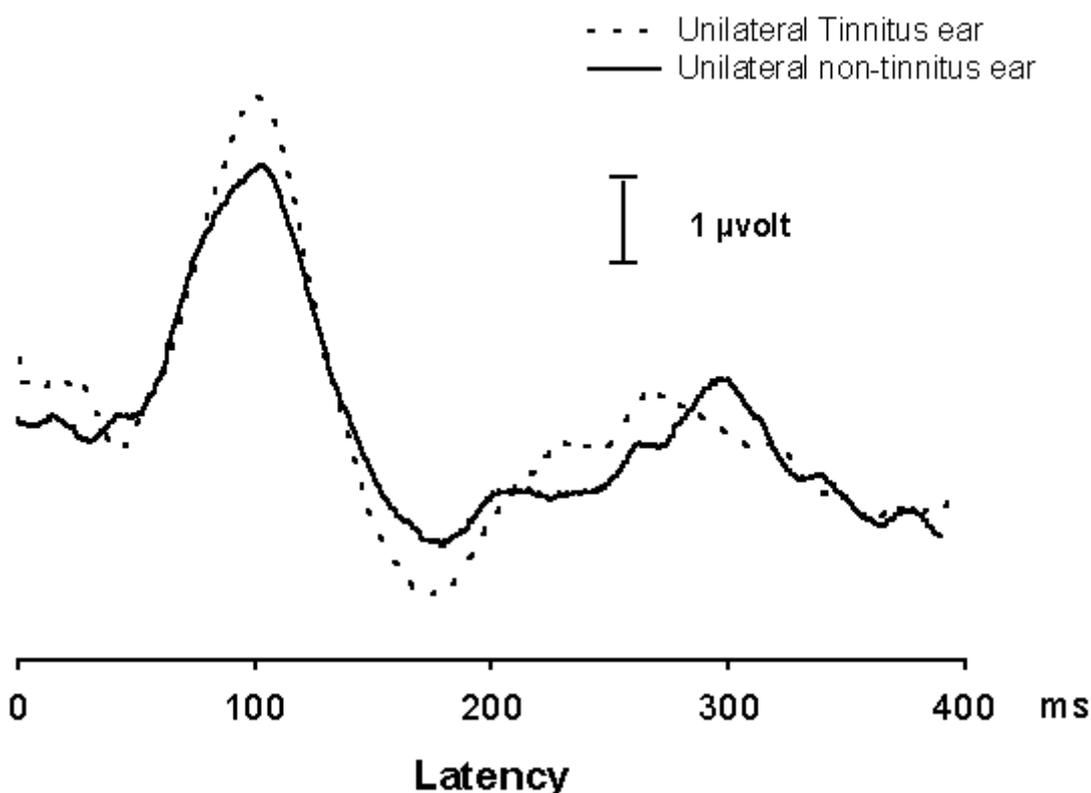


Figure 1 Grand average of auditory evoked potentials obtained at 90 dB SPL in subjects suffering from unilateral tinnitus: comparison between tinnitus ears and non-tinnitus ears ($n = 9$).

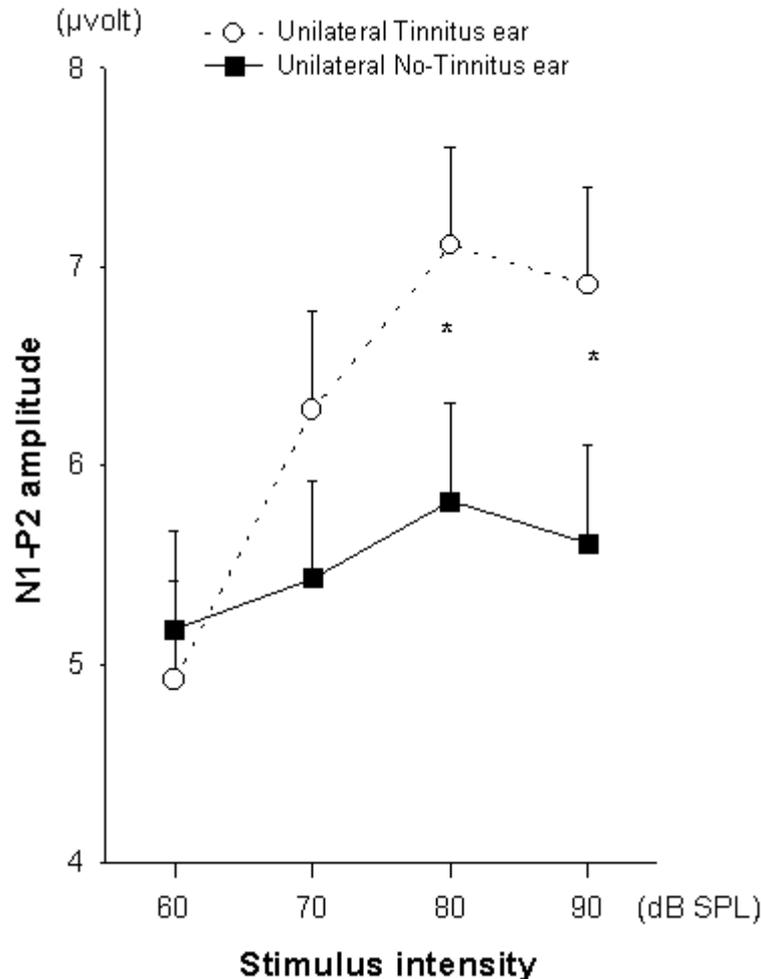


Figure 2 Mean N1-P2 amplitude (SEM) of late auditory evoked potentials, at the various stimulus intensities, in 9 unilateral tinnitus patients when tinnitus ears and non-tinnitus ears are stimulated by a 1000 Hz pure tone burst.

5 subjects of the 9 subjects studied. The effect perhaps is too small to be evident in all individuals. However, when data are averaged across subjects, there is a clear difference between the tinnitus and contralateral ears. Hoke *et al.* [1,2] reported also, in unilateral tinnitus sufferers when compared to control subjects via magnetoencephalography, that the M100 wave (the equivalent of our N1) was significantly larger, and the M2 wave (the equivalent of our P2) occurred later. The M200/M100 amplitude ratio was significantly smaller. These authors however stimulated the non-tinnitus ear and recorded the auditory evoked cortical magnetic fields contralaterally. The results of Hoke *et al.* [1,2] failed to be confirmed by Jacobson *et al.* [3] or Colding-Jorgensen *et al.* [4] who found no specific tinnitus-related characteristics and by our own present results in term of difference about P2 latency. The discrepancy between our findings and those of Jacobson *et al.* [3] and Colding-Jorgensen [4] might be attributable to methodological differences and perhaps to the level of stimulation. It is actually at relatively high stimulus intensities (80 dB SPL and 90 dB SPL) that we observed a difference between the

two ears; the level of stimulation used by Jacobson *et al.* [3] for example, was relatively low (60 dB SPL).

Salvi *et al.* [10] observed in animals, after a tone burst-induced hearing loss, that there was an increase of auditory evoked responses in terms of amplitude and intensity-dependence. This increase was observed when the stimulus frequency used to record evoked potentials was close to the frequency of maximal hearing loss. The authors suggested that these results could be attributable to a reduction of neuronal lateral inhibition due to the hearing loss. In our study, enhanced neuronal excitability on the tinnitus side could also be attributable to a reduction of lateral inhibition, due to narrow hearing loss in high frequencies (higher than 2000 Hz) or central neuronal alteration of GABA neurons [11].

In conclusion, within unilateral tinnitus sufferers, we were able to record an enhanced activity in the tinnitus affected ears compared to the contralateral ears. We suggest that enhanced neuronal excitability and tinnitus could be related to the same mechanism, a release from neuronal lateral inhibition or other central effects.

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Hypermotility of outer hair cells: DPOAE findings with hyperacusis patients

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Patients suffering from hyperacusis and tinnitus are sensitive to all variations of sound. They react with psycho vegetative symptoms to sound-exposure of even low intensities. Audiological valuation shows high discomfort levels and pathological loudness scaling, whereas hearing thresholds are almost normal.

Hyperacusis is considered a central disturbance of auditory perception. In this study we examined possible effects on the cochlea.

Seventy-two patients with hyperacusis and tinnitus were treated in our clinic: the mean age of the patients was 35.9 years (17–59), 53% were male, 47% female. They had bilateral tinnitus in 73%, left ear tinnitus in 20% and right ear tinnitus in 7% of all cases. Mean Tinnitus frequency was 6000 Hz, in 66.2% its character was tonal. Hearing thresholds were normal in all the patients, with a maximum of hearing loss not more than 15 dB (HL).

We recorded distortion product otoacoustic emissions (DPOAE) on a high resolution basis with a constant primary tone frequency ($f_2/f_1 = 1.19$), covering a primary tone frequency range between $f_2 = 488$ and 8008 Hz and a level range between $L_2 = 20$ and 65 dB SPL.

In particular we examined the different growth behaviours: 49 patients (68%) showed abnormally steep growth functions with normal DP-emissions, thus indicating signs of hypermotility of outer hair cells or hyperactivity of the cochlear amplifier.

Twenty five percent of the patients had normal DPOAE and growth functions, only 5 patients (7%) had steep slopes of growth function and low emission levels, indicating a hypofunction of the cochlea.

Our findings indicate, that 68% of our patients suffering from hyperacusis showed pathological DPOAE measurements and signs of cochlear hyperactivity.

We interpret these findings as an efferent over-stimulation of outer hair cells. This can be a sign or a result of hyperacusis as a central auditory processing disorder.

Introduction

Hyperacusis is defined as an oversensitivity to external sounds. It has to be differentiated from *phonophobia* and *recruitment*. In *phonophobia* the sensitivity is of a more psychic origin and is only produced by certain, negatively experienced sounds; *recruitment* is due to lack of outer hair cell modulation with inner ear diseases and results in an oversensitivity to frequencies of the hearing-loss.

In hyperacusis patients react to every sound with vegetative symptoms such as rise of blood pressure, increase of heart rate and sweating or change of skin turgor. Existing tinnitus mostly increases in

intensity for a certain time after noise-exposure. Diagnostic features of hyperacusis are:

- diminished discomfort levels,
- pathological loudness scaling,
- often normal hearing threshold,
- uni- or bilateral tinnitus.

Almost 50% of our tinnitus-patients suffer from hyperacusis [1], Jastreboff and Hazell [2] report similar figures.

Social consequences from hyperacusis are severe: avoidance of loudness in any form, such as music, festivities, cinema, groups and more and more normal acoustic surroundings, followed by complete social isolation. Patients show typical symptoms of generalized fear.

In literature little is to be found about hyperacusis, only Jastreboff *et al.* [3] mention hyperacusis in connection with tinnitus.

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Audiological diagnostic findings are rare and seldom reported.

Analogue to tinnitus we suggest that one reason for hyperacusis might be lack of modulating capacity of the auditory system, when incoming information is processed through the auditory pathway without sufficient efferent inhibition. It therefore is a disturbance of central auditory processing, with an inhibitory deficit in any part of the auditory pathway, even the cochlea [4].

In many audiological examinations with tinnitus patients, mainly DPOAE, we observed signs of *hypermotility of outer hair cells* [5]; this was interpreted as a cochlear "overamplification". Therefore we looked for similar audiological signs of hair cell hyperactivity in patients with hyperacusis.

Methods:

We examined 72 patients that were admitted to the hospital for indoor treatment from 1998 to 1999. Audiological testing consisted of pure tone thresholds, speech audiogram, impedance, BERA, discomfort levels and loudness scaling, tinnitus evaluation and recording of DPOAE. Distortion products were measured with resolution and a constant primary tone frequency ratio ($f_2/f_1 = 1:19$), covering for f_2 a frequency range between 488 and 8008 Hz, using Cub[®]disTM/Etymotic Research (ER-10C) instrumentation (Mimosa acoustic, NJ). Stimuli were applied in ten steps with levels from $L_2 = 65$ to 20 dB SPL, L_1-L_2 increasing with decreasing primary tone level according to the equation $L_1 = 0.4 \times L_2 + 39$ dB [6]. DP-grams and DP I/O functions were reconstructed from the recorded data. DP growth function were calculated from the slope of these functions between $L_2 = 40$ and 60 dB SPL [5]. All findings were compared to normal hearing non-tinnitus, non-hyperacusis subjects' data recorded with the same paradigm and instruments.

For this study we only examined patients with a normal hearing threshold. Hyperacusis was diagnosed through pathological loudness scaling and low discomfort levels as well as anamnestic evaluation.

DPOAE findings were classified in three groups:

- Normal DP gram and growth function,
- normal to high DP emissions and steep growth functions (hypermotility),
- low emission levels with steep growth functions (hypomotility).

Results

The mean age of our patients was 35.9 years (17–59), 53% were male, 47% female. Tinnitus was bilateral in 73%, located in the left ear in 20% and the right ear in 7% of all cases. The mean tinnitus frequency was 6000 Hz, for 66.2% of the patients it was tonal.

Hearing thresholds were normal in all patients, with a maximum hearing loss of >15 dB (HL).

According to DP growth functions

- 49 patients (68%) showed normal to high DP levels and increased slopes of I/O functions,
- 25 % (18 patients) had normal DP emissions and growth functions,
- 5 patients (7%) had decreased DP levels and increased slopes of growth function.

Discussion

In general it is assumed, that outer hair cell activity is the source of DP [7,8]. Decreased DP levels and increased growth functions seem to be proof of diminished sensitivity and tuning of the cochlear amplifier. Increased DP emissions and increased slope of I/O functions, however, seem to reflect a specific impairment in outer hair cell micromechanics, where a reinforced distortion generates and might be responsible for some type of tinnitus.

Similar to these findings with tinnitus patients [9,10] our data shows the same effect with 68% of normal hearing hyperacusis patients. Whereas in tinnitus patients without hyperacusis this inverse reaction or hypermotility of hair cells is restricted to the tinnitus frequency, in hyperacusis patients it seems to reflect a wider range of frequencies.

These results suggest, that in many hyperacusis patients some alteration of auditory processing already occurs on the cochlear level. Most probably hyperacusis as an oversensitivity to all sounds is due to an inefficient input control of sounds or even an overamplification of incoming sound [11]. This is mainly the result of disturbances in the cortical network of auditory processing that either lead to ineffective or diminished efferent control of the auditory pathway [12] or to an efferent overactivity on all levels including the outer hair cells.

Conclusion

Our results indicate that in many hyperacusis patients abnormal hypermotility of outer hair cells may occur even if hearing is completely normal. Further studies have to control these findings with therapeutic effects, especially when hyperacusis improves.

However, analysis of this data has to be intensified and compared with other audiological findings – a special software for this specific analysis is being developed and will be published.

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Masking curves and otoacoustic emissions in subjects with and without tinnitus

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There are several theories of tinnitus generation that are based on the premise that dysfunctional outer hair cell (OHC) activity results in abnormal neural activity. There have been varied efforts to show that OHCs are involved in tinnitus generation, but thus far results have been inconclusive. The goal of the present study was to determine whether dysfunctional OHCs are associated with tinnitus. Two procedures that assess OHC function are masking audiograms/curves and DPOAEs, and each of these was used in two normal-hearing groups of 12 subjects each – one with and without tinnitus. The mean masking curves showed no significant differences between groups. However, a trend was seen for the 4 and 8 kHz curves that might indicate a hypersensitive masking effect, as seen previously [2]. This same effect was particularly pronounced for subjects who had tinnitus matched to an 8 kHz pure tone. The mean DPOAE amplitudes also did not appear different between groups, but there was a consistent reduction in amplitudes seen with the input-output functions. The findings of this study did not confirm previous findings [2,3], yet differences between groups were evident. These results suggest the need for a larger-scale study to evaluate for OHC dysfunction in individuals with normal hearing and tinnitus.

Introduction

Several studies have evaluated the theory that tinnitus generation is caused by dysfunctional outer hair cell (OHC) activity. There have been varied efforts to show that the OHCs are involved, but thus far results have been inconclusive [1]. Results of two recent studies have suggested that OHC dysfunction is associated with tinnitus [2,3]. It was demonstrated that abnormal psychophysical tuning curves, characterized by hypersensitivity of the low frequency masking tones, were present in a group of subjects with tinnitus and normal hearing [2]. These masking curves differed consistently from those obtained from normal-hearing subjects without tinnitus. This increased efficiency, or hypersensitivity, to low frequency masking tones was postulated to be caused by OHC damage [4–6].

Research in experimental animals has confirmed that OHC function can be evaluated using distortion product otoacoustic emissions (DPOAEs). To follow up the findings of abnormal psychophysical

tuning curves [2], DPOAEs were measured in human subjects with normal hearing sensitivity and tonal tinnitus [3]. Two groups were tested, one with and one without tinnitus. Analysis of DPOAE data collected from these two groups revealed an unexpected result: the DPOAEs of the tinnitus group were larger than those recorded from the control group. These findings were consistent with altered OHC function in the tinnitus group.

The purpose of the present study, funded by the American Tinnitus Association, Portland, Oregon, USA, was to further evaluate the apparent phenomena of hypersensitivity to masking by low frequencies and altered DPOAEs in individuals with tinnitus and normal hearing sensitivity. The long-term goal of this project is to determine whether dysfunctional OHCs can result in tinnitus.

Methods

Subjects. Subjects with tinnitus and normal hearing sensitivity were recruited from the Tinnitus Data Registry, a database of patients who have attended the Tinnitus Clinic at the Oregon Health Sciences University, Portland, Oregon. They were selected on the basis of bilateral hearing thresholds 25 dB HL or better at frequencies 0.25, 0.5, 1, 2, 3, 4, 6

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and 8 kHz. Subjects with tinnitus who completed the study included nine males and three females (mean age 43.2 years). Control subjects included five males and seven females (mean age 43.7 years).

Equipment. Conventional hearing thresholds (0.25–8 kHz) were obtained with a Virtual model 320 audiometer. The automated tinnitus testing system that is described in a companion paper (see “Fully automated system for tinnitus loudness and pitch matching”) was used for the present study to obtain the masking curves. New software was programmed to enable the masking curves to be obtained in a fully computer-automated fashion.

The Intelligent Hearing Systems DPOAE was used to obtain distortion product otoacoustic emissions (DPOAEs), using a modified ER-2 earphone. The earphone was modified to extend the frequency range and output levels using an ER-10b Etymotic Research probe mic. The DPOAE system was housed in an IBM Thinkpad 760e laptop with baystation.

Procedures. For all subjects, hearing thresholds were obtained at 0.25, 0.5, 1, 2, 3, 4, 6 and 8 kHz. For subjects with tinnitus, the inclusion criteria included one ear with hearing thresholds 25 dB HL or better at all test frequencies, and stable, tonal tinnitus in the same ear. Control subjects had to meet the same criterion for hearing sensitivity.

For the tinnitus subjects, tinnitus pitch matching was performed using the Manual method described in the companion paper “Tinnitus loudness and pitch matching: various techniques with a computer-automated system.” Conventional masking curves (a.k.a. masking audiograms) were obtained using pure tone maskers at 1, 2, 4 and 8 kHz, as well as at the tinnitus pitch match frequency. Conventional masking curves were measured rather than psychophysical tuning curves in order to avoid exposing subjects (especially those with tinnitus) to the high sound pressure levels required for psychophysical tuning curves [7].

Masking curve test frequencies surrounding each center frequency are shown in Table 1. Thus, thresholds in the presence of each masker were determined at the frequency ratios shown in Table 1. Frequency ratios were selected to adequately sample the high and low frequency tails of the masking curves at frequencies equivalent to tips and tails of psychophysical tuning curves.

For each subject, masking curves were obtained first at 1 kHz, followed by 2, 4 and 8 kHz, and the tinnitus frequency. To obtain a masking curve, the unmasked thresholds were first determined at the

frequencies surrounding the center frequency, as shown in Table 1. The stimulus used was a pair of pure tones, 250 msec each with 25 msec rise-decay times, separated by 200 msec off-time. Thresholds were first bracketed with an up-5 dB, down 10 dB procedure. Final threshold was determined with 1 dB resolution, using an up 1 dB, down 2 dB procedure. This threshold procedure has been described in detail [8].

After thresholds in quiet were obtained at each frequency, they were reevaluated in the presence of a masking tone (i.e., simultaneous tone-on-tone masking). The frequency of the masker tone was fixed, and was 1100 msec in duration with 25 msec rise-fall times. The paired threshold stimuli were gated at 200 and 650 msec relative to the masker onset. The masker tone was presented at a level 25 dB above the unmasked threshold. The paired “maskee” tones were varied in 2 dB steps until the subject responded that they heard the paired tones clearly. At that point the level of the paired tones was raised or lowered in 1 dB steps to obtain a final masked threshold with 1 dB precision.

DPOAEs were obtained over the frequency range 783–15,800 Hz. DPOAE data were collected in the form of DP-grams, which displayed levels of emissions elicited by constant-level primary tones as a function of the frequency f_2 . In measuring the DP-gram, the f_1/f_2 ratio that describes the frequency separation of the primary tones was kept constant at 1.2. DP-grams at four stimulus-level conditions were measured. For f_1/f_2 they included 75/65, 65/55, 55/45 and 45/35 dB SPL.

RESULTS

Figure 1 shows the mean hearing thresholds, displayed separately for the tinnitus group and the non-tinnitus group. A two-way factorial ANOVA with repeated measures on the second factor (frequency) determined that there were no significant differences in mean thresholds between groups ($p > 0.05$).

Figures 2 and 3 display the mean masking curves at 4 and 8 kHz, respectively, for each group (1 and 2 kHz mean masking curves not shown). Each point represents the difference between the masked and unmasked thresholds, i.e., the “threshold shift” at each frequency. A two-way factorial ANOVA with repeated measures on “frequency” revealed that differences in mean thresholds between groups were not significant at any of the test frequencies 1, 2, 4

Table 1 Test frequencies used to obtain masking curves

| Center Frequency (Hz) | Masking Curve Frequency (Hz) | | | | | | |
|-----------------------|------------------------------|--------|--------|--------|--------|--------|--------|
| | (0.22) | (0.33) | (0.66) | (0.90) | (1.05) | (1.15) | (1.30) |
| (Multiplier) | | | | | | | |
| 1000 Hz | 220 | 330 | 660 | 900 | 1050 | 1150 | 1300 |
| 2000 Hz | 440 | 660 | 1320 | 1800 | 2100 | 2300 | 2600 |
| 4000 Hz | 880 | 1320 | 2640 | 3600 | 4200 | 4600 | 5200 |
| 8000 Hz | 1760 | 2640 | 5280 | 7200 | 8400 | 9200 | 10400 |

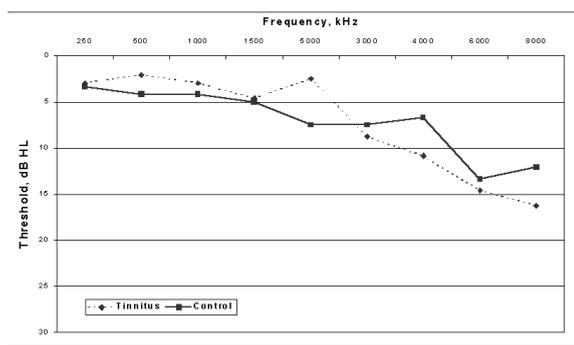


Figure 1 Mean hearing thresholds shown separately for tinnitus and non-tinnitus groups.

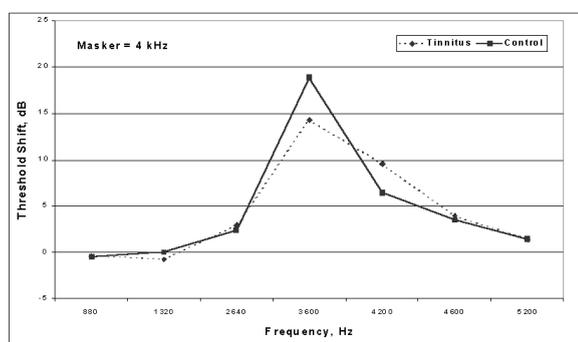


Figure 2 Mean masking curves centered at 4 kHz for both groups. Each point represents the difference between masked and unmasked thresholds.

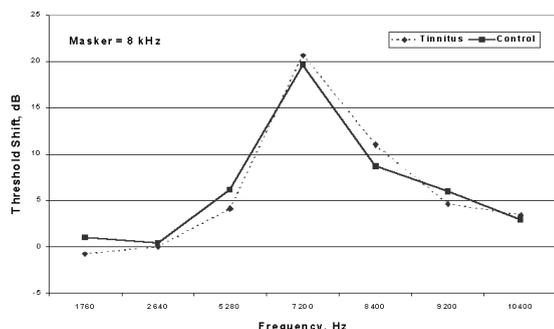


Figure 3 Mean masking curves centered at 8 kHz for both groups.

or 8 kHz ($p > 0.05$). It should be noted, however, that the threshold difference at the frequency just above the center frequency was higher for the tinnitus group at 4 and 8 kHz. This is the area on the masking curve that such a difference would be expected if there were hypersensitive masking effects.

Figure 4 shows the mean masking curves for three tinnitus subjects who made pitch matches at 8 kHz, along with the mean 8 kHz masking curve for the 12 control subjects. Because of the unequal N between groups, statistical analysis could not be

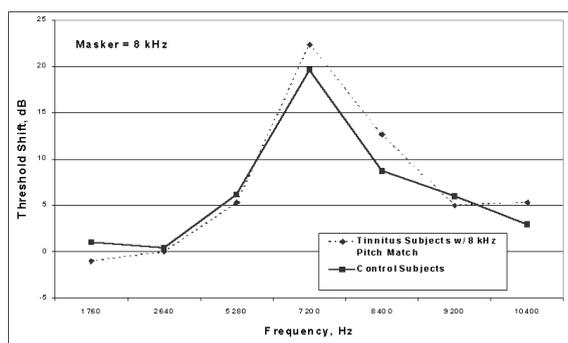


Figure 4 Mean masking curves centered at 8 kHz for the three subjects who pitch matched their tinnitus to an 8 kHz tone, and the 12 control subjects.

conducted. However, there is again seen an increase in the threshold shift for the tinnitus subjects at the frequency immediately above the center frequency. This effect was particularly pronounced for subject B48 (see Figure 5).

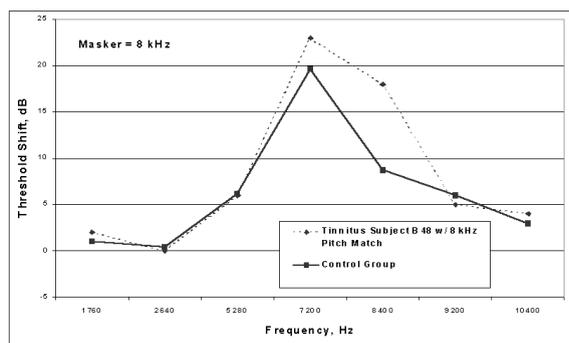


Figure 5 Masking curve centered at 8 kHz for subject B48, who made a pitch match at 8 kHz, and mean masking curve for the 12 control subjects.

Figure 6 shows the mean DP-grams for both groups of subjects. It was not possible to statistically determine if there were differences between groups, because of the large number of missing data (where no DPOAE responses were obtained). Visual inspection, however, suggests that there were no differences.

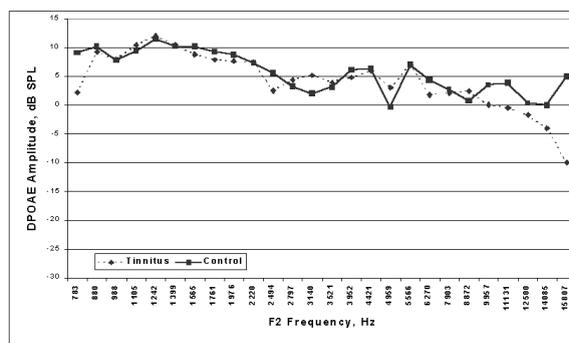


Figure 6 Mean DP-grams for tinnitus and non-tinnitus groups.

Figures 7, 8 and 9 show intensity functions for DPOAEs at 1976 Hz, 3952 Hz, and 7903 Hz, respectively. These frequencies were chosen to represent low, mid, and high frequency areas of the DP-grams. It can be seen that in each case, the tinnitus group provided lower mean amplitudes than the control group.

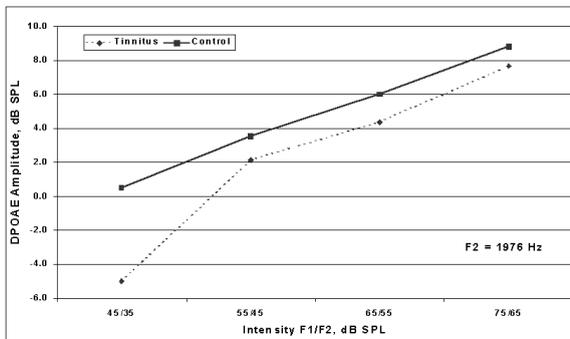


Figure 7 Input-output functions for DPOAEs at 1976 Hz.

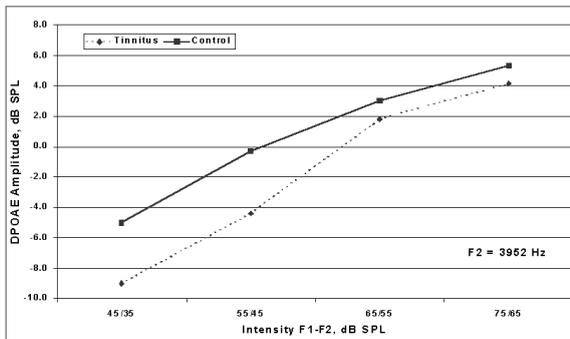


Figure 8 Input-output functions for DPOAEs at 3952 Hz.

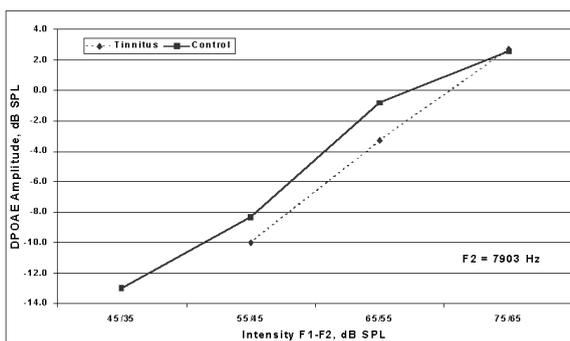


Figure 9 Input-output functions for DPOAEs at 7903 Hz.

Discussion and conclusion

The present study was conducted because it was hypothesized that there would be differences in masking curves and DP-grams between groups of normal-hearing subjects with and without tinnitus. The data show that mean masking curves and mean DP-grams were not different between groups at any

of the frequencies tested. However, further inspection of the data showed interesting trends.

First, for the mean masking curves at 4 and 8 kHz, the test frequencies immediately above the center frequencies showed elevated threshold shifts for the tinnitus subjects relative to the controls. This would be the expected result if this study showed the same effect that was noted previously [2]. In that study, the low-frequency tails for psychophysical tuning curves were shifted downward for the tinnitus subjects relative to the control subjects. This indicated that the lower frequency tones had an enhanced masking effect on the probe tone that was fixed at a higher frequency.

In the present study, masking curves, also known as masking audiograms, were obtained rather than psychophysical tuning curves. Masking curves were used to prevent the presentation of stimuli at high levels which are often uncomfortable for individuals with tinnitus [7]. Masking curves correlate quantitatively with tuning curves, as described by Zwicker and Schorn [9].

Normal tuning curves typically show a long low-frequency tail due to upward spread of masking. This same masking effect occurs for masking curves, but the extended "tail" is seen at frequencies *above* the center frequency where a fixed tone serves as the masker. However, this high-frequency extension is typically only seen at masker levels above 40 dB SL (see Figure 1 from [9]). At the level used in the present study (25 dB SL), the masking effect was greatly reduced, with slight asymmetry extending to the lower frequency region. It seems likely that conventional masking curves at the masker level tested (25 dB SL) were not as sensitive to outer hair cell dysfunction as the psychophysical masking curves. This study should therefore be replicated using higher level masking tones to obtain masking curves.

In spite of the lack of significant differences between mean masking curves, there appeared to be a trend for an enhanced masking effect at the frequency immediately above the center frequency. This was seen for the mean masking curves at 4 and 8 kHz (Figures 2 and 3). It was also seen with the three subjects who matched their tinnitus to an 8 kHz tone (Figures 4 and 5). It is therefore plausible that with a larger sample size (and hence greater statistical power) these trends would become significant.

The mean DP-grams indicated no differences in DPOAEs between the two groups. However, the DPOAE intensity functions showed a consistent trend for the mean DPOAE amplitudes to be lower for the tinnitus group than for the control group (Figures 7, 8 and 9). This trend contrasted with the *enhanced* DPOAEs seen in normal-hearing tinnitus subjects previously [3]. Elevated amplitudes might indicate disinhibition of the efferent pathways, whereas reduced amplitudes might suggest that the outer hair cells themselves are dysfunctional. It should be noted that in the present study, a different and larger group of subjects was used. Also, DPOAE measures were improved in the current

study to eliminate artifacts such as nonlinearities in the sound field, and to increase the signal-to-noise ratios. Also, a different DPOAE unit was used. Clearly, DPOAEs must be evaluated in a larger sample to resolve these apparent discrepancies.

Any group of subjects with tinnitus probably includes tinnitus originating at different levels of the auditory system, from peripheral to central. The previous studies that evaluated outer hair cell function in tinnitus subjects with normal hearing [2,3], and the present study, would be considered small-N studies. Thus, the different groups tested may have had different types of tinnitus. Procedures and equipment also varied between studies. These studies therefore should each be reexamined with respect to all relevant methods and results, with recommendations made to conduct a more definitive study. Such a study, using a larger number of subjects, would help to resolve the question of outer hair cell dysfunction in individuals with tinnitus.

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Intracranial pressure as a generator of aural noises: Improved differential diagnosis will facilitate effective treatments

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Raised cerebral fluid pressure (intracranial hypertension) often results in tinnitus, vertigo and sometimes a hearing loss, which may be irreversible. In cases where the expected headache and papilloedema are absent, patients with intracranial hypertension are likely to be referred to the otolaryngological clinic for investigations of the audiovestibular symptoms, yet these patients are rarely cross-referred to neurology.

A multi-centre study which is supported by 'Defeating Deafness – the Hearing Research Trust' is currently underway. This study aims to more clearly define the characteristics of the tinnitus, vertigo, aural fullness and hearing loss found with intracranial hypertension. From this work a questionnaire and objective clinical tests such as made by the 'TMD Cerebral and Cochlear Pressure Analyser' will be combined to provide an 'At Risk Profile' to facilitate cross-referral of patients with intracranial hypertension to neurology.

Certain aspects of this multi-centre study are discussed. Two case studies highlight inappropriate diagnosis of intracranial hypertension as otological disorders. Low frequency tinnitus of a pulsatile and/or 'whooshing' 'sea-like' nature appears to be the key symptom for diagnosing intracranial hypertension and in many cases may be the only defining symptom. The existence of a cohort of mostly female patients with these symptoms, which are due to undiagnosed intracranial hypertension, has both a cost implication for the health service and is a 'quality of life' issue for the individual. Correct diagnosis of intracranial hypertension in the otolaryngological clinic is important to avoid ineffective treatments. It also allows recognised treatments and management regimes to be applied which should provide the patient with total relief from audiovestibular symptoms.

Introduction

It is recognised that raised cerebral fluid pressure (intracranial hypertension) often results in aural noises, dizziness and sometimes a hearing loss, which may be irreversible. It is apparent that patients with intracranial hypertension are being missed in virtually all otology clinics, since the few centres which look to identify these patients, find them. Currently in nearly all cases the condition will be wrongly diagnosed as being a 'Ménière's like' or a non-specific inner ear disorder which may include tinnitus as the primary symptom. Yet this condition is treatable if correctly diagnosed, with often a complete remission of the audiological symptoms.

There is a particular interest in the audiovestibular symptomatology of patients with a condition

known as Benign Intracranial Hypertension (BIH) also known as pseudotumour cerebri or idiopathic intracranial hypertension [1]. How do we differentiate these patients with this condition from those with an actual otological disease process? How common is this problem and what are the referral patterns? What are the effective diagnosis and treatment regimes? What are the underlying mechanisms for this disorder and in particular the intracranial-labyrinthine interactions?

A multi-centre UK study funded by 'Defeating Deafness – the Hearing Research Trust' is beginning to address some of these questions. This collaborative action includes: the NIPA (Non-invasive Intracranial Pressure Assessment) Unit, Southampton; the Department of Neuro-Otology, National Hospital for Neurology and Neurosurgery, London; the Academic Department of Neurosurgery and the Department of Neuro-Otology, Addenbrooks,

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Cambridge; the Queens Medical School and Institute of Hearing Research, Nottingham.

These centres will research the exact nature of the symptomatology and utilise a non-surgical method of assessing the cerebral and cochlear fluid pressure on patients with proven intracranial hypertension (the MMS-11 TMD Cerebral and Cochlear Pressure Analyser). The aims are: (1) to advance our understanding of inner ear physiology by testing the hypothesis that *'Connectivity between the cerebral and cochlear fluids is associated with specific forms of tinnitus, vertigo and hearing loss'*, and (2) to provide an 'At Risk Profile' to help all major audiology and neuro-otology clinics identify and successfully treat patients with this condition.

This paper provides a résumé of the methods being employed in this multi-centre trial and illustrates the importance of this work in terms of two patients who were wrongly diagnosed as having otolaryngological disorders and were later found to have BIH.

The clinical study

In the current multi-centre trial, patients with confirmed raised intracranial pressure and in particular with BIH are being cross-referred from neurology/neurosurgery to the audiology and neuro-otology centres of the participating hospitals. A full neurological assessment is made on these patients and BIH is diagnosed on the basis of absent cerebral lesion and tumours, normal ventricle appearance, cerebrospinal fluid (CSF) of normal composition and abnormal high CSF on lumbar puncture. A complete assessment of visual acuity, visual fields and enlarged blind spots is also made and papilloedema is almost always present.

Once diagnosed as BIH, these patients undergo an audiological assessment and a detailed questionnaire is administered by the researching clinician to assess the nature and severity of any tinnitus, dizziness, head and aural fullness, hearing deficits, visual obscurations, headache and the patient's general feeling of wellbeing.

A non-invasive measurement of the cochlear pressure is made using the 'MMS-10/11 TMD Cerebral and Cochlear Pressure Analyser' which is also used to quantify the level of cardiovascular noise being emitted from the external ear canal [2,3,4]. Cerebral to cochlear fluid connectivity is also assessed by inducing a change in intracranial pressure by moving the patient from a sitting upright to supine position [5,6]. A corresponding change in cochlear pressure is assumed to represent a patent fluid pathway between the cerebral and cochlear fluids. The relationship between the change in pressure with posture and the existence of tinnitus and cardiovascular activity in a particular ear will be investigated to see if a patent cerebral-cochlear fluid pathway is a prerequisite for having low frequency tinnitus, and possibly stimulation of the cochlea directly by cerebral pressure waves.

The aim is to test up to 48 patients with BIH,

with each of the 4 centres contributing about 12 patients. In addition, the symptom questionnaire devised for the BIH patients has also been answered by an age and gender matched control group of 60 normal female subjects. These subjects have undergone a full TMD cerebral/cochlear pressure, hearing and tympanometric assessment.

Early results

To date 60 normal female controls and 10 BIH subjects with proven intracranial hypertension have been tested at Southampton. It is not possible to draw definite conclusions at the current time, nevertheless, the findings to date are in general agreement with the earlier Southampton study which included 34 BIH patients [7]. In this earlier study an open fluid connection between the cerebral and cochlear (perilymphatic) fluids could be demonstrated using the 'TMD Cerebral and Cochlear Fluid Pressure Analyser' in 29 patients. Of these patients 16 (55%) complained of tinnitus which was unilateral in 6 (21%) cases and it was bilateral in 10 (34%) cases. As in the current series, if tinnitus exists it is principally of a low frequency nature with pulsatile characteristics in some instances.

Comparing these findings with the normative data, none of the 60 normal females questioned reported daily headaches, low frequency or pulsatile tinnitus as found in most, but not all of the BIH patients.

Case studies

The multi-centre study seeks to investigate the premise that patients with intracranial hypertension are being seen for otological conditions, but are not being cross referred to neurology. Of the 10 patients seen in the current series, it is interesting to note that 2 patients were being seen by ENT consultants who were treating the patients for otolaryngological disorders. In both cases, only by chance the patients visited their opticians for a regular check-up, and the opticians fortunately identified papilloedema and immediately referred them to our Wessex Neurological Centre where BIH was confirmed.

Case 1

The first case is a slightly over-weight 18 year old female who had been studying for her A levels when one morning she woke up with a 'whooshing' tinnitus in her left ear (November 1997). This was described as being like 'a fast train' noise which was incidental with her heart beat. She noticed that the tinnitus stopped when turning her head, but became worse with physical activities such as squash. The 'whooshing' tinnitus was always present and frequently interfered with daily activities and sleep. She did not have any balance problems, no sensations of pressure or fullness, and no significant headaches.

The patient's GP referred her to an ENT consultant so that the pulsatile tinnitus could be investigated further (15/01/98). The ENT consultant found no clinical abnormalities and the audiogram was normal. The CT scan was normal and it was decided to undertake a neurological vascular examination.

About 8 months after the start of the condition the patient visited her optician for a regular check-up and he found bilateral papilloedema (25/06/98). She was immediately referred to our Wessex Neurological Centre where the TMD technique was used to provide a non-invasive assessment of the intracranial pressure and to assess patency of the cerebral-cochlear fluid pathways (26/06/98). There appeared to be a cerebral-cochlear connection in the left ear where the tinnitus was present but not the right ear which was without tinnitus. A lumbar puncture gave an excessive opening pressure of 46 cm of saline. The CSF composition, cell count, glucose and protein were all normal and BIH was diagnosed. Interestingly she commented that the tinnitus was no longer present 2 to 3 weeks after the lumbar puncture.

The patient was managed on oral diuretics, Frusemide (40 mg per day), for 4 weeks and then a repeat lumbar puncture showed that the CSF pressure was still raised at 38 cm saline. At this time 10ml of CSF was withdrawn which brought the pressure down to 26 cm saline. The papilloedema still was present (14/08/98). A course of steroid (30 mg per day Prednisolone) was taken for 1 week and then Frusemide was continued. Ten weeks later there was no papilloedema and the fundi were normal (20/10/98). The opening lumbar puncture pressure was lower, but still abnormally high at 29.5 cm. These findings were repeated after a further 10 weeks following a continuing course of Frusemide (40 mg alternative days).

The diuretic was discontinued and when she was reviewed this year her optic disks were normal (12/05/99). At this time TMD assessment of intracranial pressure was used so as to avoid further lumbar puncture, and this indicated there had been a significant reduction in CSF pressure although this pressure may still be greater than normal. The tinnitus was no longer continuous and only occurred 3 to 4 times per month. The character of the tinnitus had changed from the 'train-like' whooshing tinnitus to an occasional less intrusive muffled 'whooshing'. On the basis that the optic disks were normal, the patient has now been discharged and will be reviewed by her GP at regular intervals.

Case 2

This patient is a 35 year old female civil servant who was first referred by her GP to an ENT consultant because of a sensation of aural pressure in both ears, a low frequency fluctuating hearing loss, vertigo and tinnitus which was described as a 'buzzing' (6/01/97). The vertigo was episodic, objective and rotary. Vertigo attacks occurred every few weeks and these

could sometimes last all day. The vertigo was accompanied by the tinnitus. The patient felt nauseous during these attacks and vomited on a number of occasions.

The patient was reviewed later in 1997 by the ENT consultant who found that a mild low frequency hearing loss had developed over a period of 11 months since the last audiogram as shown in Figure 1. The other symptoms remained largely unchanged and the patient complained that she found the blockage of her ears extremely irritating (14/11/97). Neither Beconasefi nor topical steroids improved the condition that was considered to be related to nasal obstruction. The consultant considered the condition to be due to persistent Eustachian tube function with nasal obstruction. ENT surgery was undertaken in terms of trimming of turbinates to clear the nose and septoplasty.

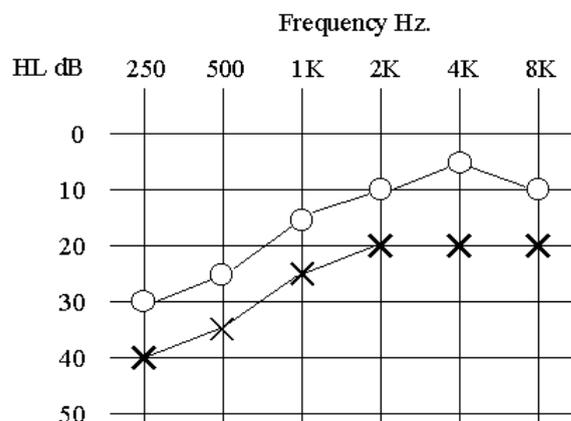


Figure 1 Audiogram for a 35 year old patient with intracranial hypertension which shows a mild low frequency loss

Following this surgery the symptoms continued but were less severe. However, 16 months later the patient was admitted into hospital due to a sudden onset of headache and nausea (16/03/98). The dizziness was now occurring regularly, particularly in the morning. There did not appear to be papilloedema and the CT scan was normal. Following investigation the patient was discharged and was prescribed Serc[®], 16 mg per day for 1 month.

In February 1999 the patient visited her optician who found papilloedema and immediately referred her to the Wessex Neurological Centre (9/02/99). At this time she reported headaches with visual disturbances, vomiting and diarrhoea. These attacks lasted up to 1 hour and were sometimes accompanied by 'bright flashing lights'. Over the past 12 months the rotary vertigo had become less severe and now only lasted about 10 minutes, however, she now had periods when she became unsteady on her feet and had a more general feeling of dizziness. This was described 'as feeling drunk' and she frequently 'bumped into things'. Absent acoustic stapedial reflexes precluded TMD assessment.

Over the past 3 months she had noticed a change in her vision in terms of transient blindness which lasted a few seconds and sometimes blurring which

lasted a few minutes. She also commented that her night vision had deteriorated and had a feeling of 'bruising' behind her eyes. On investigation bilateral papilloedema and field defects were found. Lumbar puncture found a raised CSF pressure of 28 cm saline. The diagnosis of BIH was therefore made (10/02/99). The condition is not responding to medication (Acetazolamide) and a lumbar-peritoneal shunt with possibly optic nerve fenestration is being considered.

Discussion and conclusion

It is evident that the otolaryngological symptoms associated with intracranial hypertension can include tinnitus, dizziness, vertigo, a hearing loss which may fluctuate, and a sensation of aural fullness. Depending on the combination and exact nature of these symptoms, intracranial hypertension may be misdiagnosed as Ménière's disorder, non-specific labyrinthine disorders, Eustachian tube dysfunction and even nasal obstruction. Correct differential diagnosis depends on identifying the underlying signs and symptoms of intracranial hypertension, however, this is seldom possible, even by those experienced in neurology, without reverting to lumbar puncture. The situation is even more complex since we know that most cases intracranial hypertension will occur without the expected pressure-specific headache and papilloedema will either not be present or will go undetected. This may leave the otolaryngological symptoms as the main reason for referrals from the GP to the specialist consultant.

The two cases presented in this paper are good examples of the above. Both were initially referred by their GPs to an ENT consultant to investigate a 'whooshing' tinnitus in the first case and in the second case a combination of tinnitus, dizziness and sensations of aural pressure. With the first patient, one of the key symptoms of intracranial hypertension, headache, was not present and with the second patient, headache was initially not considered to be significant and at a later stage was considered to be nothing more than migraine. Although headaches are the most common symptom found with intracranial hypertension they are not infrequently absent, mild or non-specific. Also headaches often accompany vertiginous episodes or tinnitus. Rassekh and Harker (1992) report that 22% of Ménière's patients suffer from migraine and this increases to 81% for those with so-called vestibular Ménière's [8].

Visual problems and papilloedema are further important pointers to underlying intracranial hypertension. However, in one of the few otolaryngological clinics where BIH is regularly diagnosed, Sismanis found that only 4/20 (20%) of patients reported actual visual problems [9]. It is also recognised that the absence of papilloedema may not be taken to indicate the absence of raised intracranial pressure [10]. Furthermore, papilloedema is unlikely to be seen in cases where abnormal

pressure is episodic in nature. It is reported that clinically significant changes in the fundus which are recognisable as papilloedema are only apparent in a minority of patients (5–10%) with raised intracranial pressure, and then only after a prolonged period of several days or even weeks [10].

The actual prevalence of undiagnosed intracranial hypertension existing in the GP practice or the otolaryngological clinic is as yet unknown. The generally accepted low incidence of 1 case of BIH per 100,000 population per year cited by Wall and George cannot be taken as representative of undiagnosed intracranial hypertension which is likely to be significantly more common in certain groups of the population for a number of reasons [11]. Firstly, the condition mostly affects women within the age range of 14 to 45 and there will be a cohort of women patients in which the condition is never correctly diagnosed. Secondly, the diagnosis of BIH largely depends on a referral for papilloedema. However, as described above, for each patient with papilloedema there could be 10 or more patients with intracranial hypertension without papilloedema. Added to this, unless the visual condition is progressive, detection of papilloedema may be a perchance event dependent on a visit to a vigilant optician – of the first 10 BIH patients seen in the latest series half have been referred to neurology from opticians. Self referral by the patient is also highly unlikely, because papilloedema normal goes unnoticed unless a significant visual deficit has developed.

Correct diagnosis of intracranial hypertension in the otolaryngological clinic is important as recognized treatments and management strategies should provide the patient with total relief from audiovestibular symptoms [1,9]. Treatments include dietary management in terms of weight loss if appropriate and restricted salt intake. Medication includes diuretics such as Diamox often in combination with a short 1 week course of a steroid. Surgical treatments have been used for treating the audiovestibular symptomatology and include cerebrospinal fluid drainage by either repeated lumbar puncture or lumbar-peritoneal shunts [12]. As our understanding of intracranial/inner fluid interactions improves we are beginning to see the advent of new surgical treatments such as the posterior fossa cochlear aqueduct occlusion procedure which appears to relieve certain forms of tinnitus and vertigo [13].

The current multi-centre study aims to more clearly define the characteristics of the tinnitus, vertigo, aural fullness and hearing loss found with intracranial hypertension, Figure 2. From this a strategy will be developed whereby questionnaires and objective clinical measurements such as the TMD technique can provide an 'At Risk Profile' to help identify patients with intracranial hypertension and to allow cross-referral to neurology. If available, the TMD technique is valuable for reducing the need for lumbar puncture by providing a non-invasive alternative for assessing changes in intracranial pressure with symptoms and treatment, Figure 3. Since patients with treated intracranial

Predominantly female – at least 4 to 1, female/male ratio. The patient may be 20% or more overweight.

Typical age range – 18 to 45 years

Likely to be suffering from a low frequency tinnitus which will be described as ‘hum’, ‘roaring’, ‘whooshing’ or perhaps ‘sea like’ with sometimes characteristics which are synchronous with the heart beat. About 60% of patients will report tinnitus and of these about 60–70% (36–42% of total) will be of a low frequency type. In cases of unilateral tinnitus, gentle compression of the internal jugular vein will often result in a reduction in the intensity of the tinnitus or even a complete cessation. Likewise turning the head to the ipsilateral side will often reduce the tinnitus.

Most patients will report a mild imbalance or ‘unsteadiness on their feet’. About 40% of those with tinnitus will be suffering some form of objective vertigo. This will be described as episodes when the ‘room appears to move’ and this can last for several minutes and sometimes hours. This is often not fully developed rotary vertigo. The feeling is often associated with nausea, but only infrequently vomiting.

The patient will be suffering from a malaise which will often be associated with a ‘deterioration in memory’, ‘mental slowing’ or ‘dulling of mind’. The patient will commonly report headaches, however, in most cases these headaches will be mild, sometimes described as a ‘dull’ headache. The headache may be associated with a pressure or fullness sensations in the head, ears or behind the eyes.

If investigated, papilloedema will only probably be found in less than 10% of cases. Interestingly, although visual deficits are often found, these or visual disturbances frequently go unreported by the patient. If these occur, they may include ‘greying’ or ‘tunneling’ which may occur – as with other symptoms – with change of posture and subsequently last for several minutes.

Low frequency and/or fluctuating hearing losses are also symptoms, but only rarely are significant enough to be noticed by patients.

The most distinguishing associations of intracranial hypertension are probably ‘female’ and ‘low frequency and/or pulsatile tinnitus’. Nevertheless, if this latter symptom alone was taken for a ‘clinical screen’ for this condition, then we would expect to miss over 50% of the patients.

Figure 2: A typical profile for sub-clinical intracranial hypertension

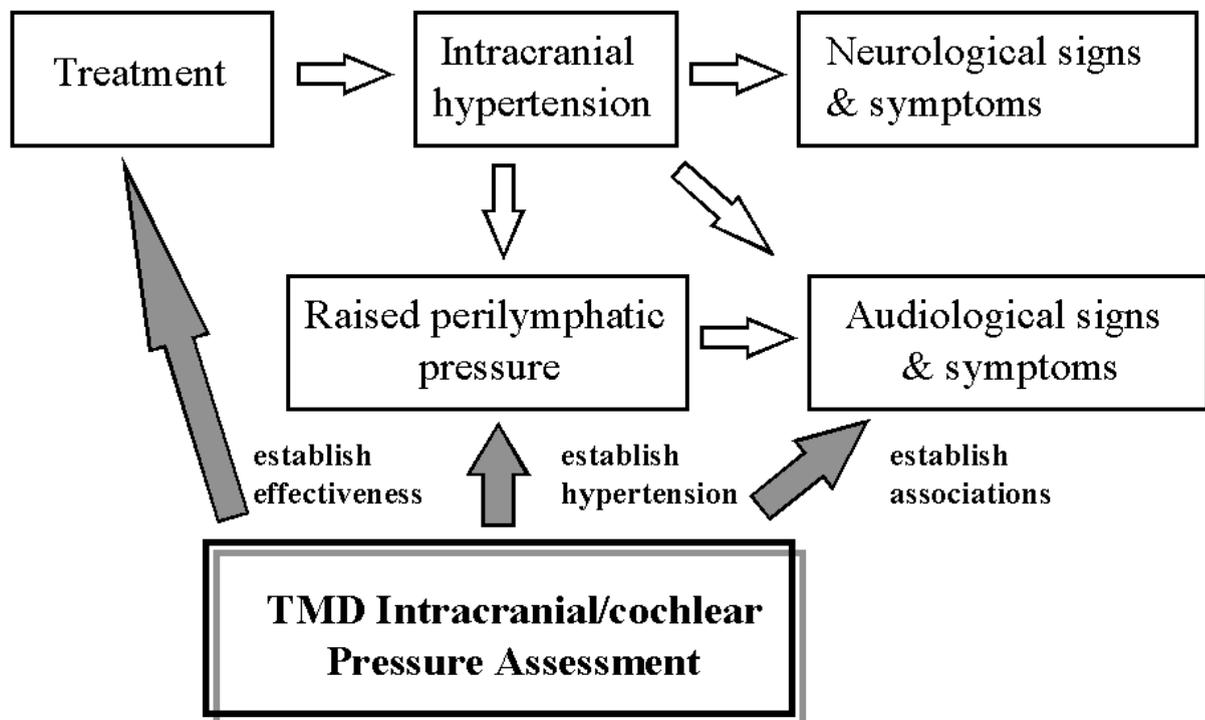


Figure 3 Clinical use of the MMS10/11 TMD cerebral and cochlear pressure analyser

hypertension remain 'at risk' of further occurrences, then the TMD technique is also proving valuable for providing pressure assessments with long term patient reviews

Low frequency tinnitus of a pulsatile and/or 'whooshing' 'sea-like' nature appears to be the key symptom for diagnosing intracranial hypertension and in many cases may be the only defining symptom. This finding concurs with the observations made by other several authors who consider that tinnitus and intracranial pressure generated aural noises may be a better indication of increased intracranial pressure than headache or visual obscurities, and indeed may be the only manifestation of this condition [9,14]. If present, gentle compression of the internal jugular vein will often reduce the intensity of the tinnitus or even cause a complete cessation. Likewise, in cases of unilateral tinnitus, turning the head to the ipsilateral side will often reduce or abolish the tinnitus. In the opinion of Sismanis, idiopathic intracranial hypertension, glomus tumors and carotid atherosclerosis are the most common aetiologies for pulsatile tinnitus seen in the otolaryngological clinic [15].

It is now recognised that the misdiagnosis of intracranial hypertension is not just occurring in otolaryngology. Recent studies show that patients with intracranial hypertension are being referred to headache clinics and the condition is being missed because of one of the key symptoms, papilloedema, is absent. In a recent study conducted at the Houston Headache Clinic all patients with refractory chronic daily headache underwent lumbar puncture even though they did not have papilloedema. Of the 85 patients, 12 (14%) were found to have raised CSF pressure [16]. In a later case-control study, 25 patients with refractory chronic daily headaches were selected on the basis that they had raised CSF pressure without papilloedema. These were compared with 60 patients with similar headaches who had normal CSF pressure. It was concluded that pulsatile tinnitus was the strongest indicator for intracranial hypertension without papilloedema [17].

The existence of a cohort of mostly female patients with undiagnosed intracranial hypertension has both a cost implication for the health service and is a 'quality of life' issue for the individual. It should be remembered that besides the symptoms described above, intracranial hypertension is normally associated with a general feeling of malaise and dulling of memory. These are disabling conditions and are often described by the patient as 'not feeling in this world' or 'feeling in a constant daze'. These symptoms alone may be so severe as to be incapacitating and to make it impossible for the patient to continue with his/her occupation. Failure to diagnose intracranial hypertension, therefore, has significant implications for the quality of life of the patient. If tinnitus is the only well defined symptom, then the apparent degree of incapacitation with this symptom may be perplexing to the clinician and there may be a danger of the patient being labelled as psychosomatic.

The outcome of the current UK multi-centre study should provide a better understanding of the pathophysiology of the audiovestibular symptomatology of intracranial hypertension, and whether this is as a direct consequence of connectivity between the cerebral and cochlear fluids [18,19]. By providing an 'At Risk Profile' to help identify patients with intracranial hypertension, the current 'Defeating Deafness' sponsored study will provide the foundation for future work to establish the prevalence and referral patterns for undiagnosed intracranial hypertension. This in turn should lead to more effective treatment with the likelihood of complete relief from various audiovestibular disorders for certain patients.

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Quality management in the therapy of chronic tinnitus

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The assessment of psychological complaint patterns has become increasingly important during the past years for studies with, and clinical management of, chronic tinnitus patients. Unlike research in the area of chronic pain, only about nine scientifically relevant questionnaires designed to evaluate the degree of tinnitus severity exist world-wide.

Method

In this presentation, all available questionnaires for the assessment of psychological tinnitus severity are summarised, and their individual advantages and disadvantages are compared and discussed critically. We find an acceptable psychometric stability only in fore questionnaires [1,2,3]. The instrument designed by Newman [4] is criticised [5]. When contrasted with other comparable instruments, we find the Tinnitus Questionnaire [TQ;6] and the Tinnitus-Fragebogen [TF;7] achieve the best evaluation results so far: The instrument allows for transcultural comparisons because of its semantical and linguistical equivalence of the English and German versions. Its high acceptance in German-speaking countries is a major advantage for the evaluation of the effectiveness of different treatment methods. Its general use has been recommended in 1997 by a scientific committee of the Germany Society of Oto-Rhino-Laryngology. Experiences collected in German-speaking countries in several evaluation studies of the TQ are reported.

Introduction

The experimental and the clinical evaluation of a patient's tinnitus are core issues in current tinnitus research and therapy. To the present day, however, no methods exist to localise and quantify tinnitus with any certainty. In order to gauge the severity of tinnitus, subjective methods such as psychoacoustic comparison measurements and self-assessment by the patient himself are the basis of scientific data. In assessing the multi-dimensional character of tin-

nitus burden, instruments which reflect bio-psycho-social aspects through a broad range of questions (items) are especially useful. Items include distraction from tinnitus, concentration, hearing difficulties, sleeping disorders, anxiety about the future, catastrophisations, psychosomatic problems, etc., which are rated by the patients.

As preconditions for quality control, generally accepted quality standards for psychometric instruments are the minimum requirement. At the Fourth International Tinnitus Seminar in Bordeaux, Erlandsson emphasised the necessity of further development and distribution of tinnitus-specific questionnaires as an indispensable test instrument in diagnostic tinnitus grading and evaluation of various tinnitus intervention studies [8]. Not all of the tinnitus questionnaires hitherto published and partially utilised in evaluation studies fulfil these preconditions.

Methods

A number of complex tinnitus questionnaires designed to assess the dimensions impairment and handicap have been developed recently, but they have not been systematically evaluated or compared.

In the following, structural characteristics of each instrument are sketched and evaluated according to a system of single appraisals of different fields of development (Table 1).

Tinnitus questionnaires like the *open-ended Tinnitus Questionnaire* [9] and similarly the *Tinnitus Problems Questionnaire* TPQ [10], are not practical core objective tinnitus questionnaires and have been excluded from the present study. We also regard the *Tinnitus Handicap/Support Scale* SHSS [11] and the *Tinnitus Cognitions Questionnaire* TCQ [12] as special cases, since they were developed to investigate very specific issues.

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Table 1 Criteria for appraisal of psychometric quality

| Psychometry | ± | -- | - | + | ++ | +++ |
|----------------------------|-----------|------|-------|-----------|-------------|--------------------|
| item selection | uncertain | | none | estimated | %-evaluated | factorial analytic |
| factorial analysis | uncertain | none | | estimated | single | multiple |
| internal consistency | uncertain | none | <0.50 | 0.50–0.75 | 0.75–0.85 | >0.85 |
| test–retest–reliability | uncertain | none | | <0.50 | <0.75 | >0.75 |
| criterion-related validity | uncertain | none | | <0.50 | <0.75 | >0.75 |
| construct validity | uncertain | none | | low | fair | good |
| objectivity | uncertain | none | | fair | good | software |
| practicability | uncertain | none | | fair | good | software |
| graduation | uncertain | none | | estimated | two-level | multilevel |
| studies | uncertain | | none | developer | other | several |
| test-cases | uncertain | <50 | <100 | <200 | <500 | >500 |
| psychometrically robust | no | no | poor | low | good | excellent |

Results

Descriptions of Tinnitus Questionnaires

Assessment

(1) The *Tinnitus Stress Test* (TST) was designed as a concise test to measure a tinnitus related stress [13]. In a study involving 60 patients were found a medium-range construct validity (7-grade “tinnitus intensity index”, 4-grade “tinnitus impairment scale”) and medium-range validity of criteria with the Zung Depression Scale [14]. The longitudinal section analysis does not fulfil the requirements of a test–retest-study.

Conclusion: Not reliable due to inadequate test construction.

(2) The *Tinnitus Severity Scale* (TSS) [15] is also not reliable. The items were derived from Hallam’s TQ, rephrased, and reassigned to the 5 scales of Hallam [6] without performing a new factorial analysis. Due to a high drop-out rate, the test–retest-results are untrustworthy.

Assessment: Not reliable due to inadequate test construction.

(3) The *Tinnitus Handicap Questionnaire* [THQ; 1] is unsatisfactory: for instance, social, emotional, and physical complaints are summarised as “psychological burden” with a correspondingly variable internal consistency. Newman *et al.* [16] were not able to confirm the high correlation of the THQ and hearing difficulties. The THQ has been employed in a cross-section study in its French translation with 281 patients [16] and only rarely in evaluation studies [18].

Conclusion: Not very reliable due to partially inadequate test construction and criticism of the composition of scales.

(4) In 1991, the *Tinnitus Reaction Questionnaire* (TRQ) is published [2]. The test quality is good, however, normal-value data for certain clinical groups are missing. Also, the questionnaire is focused one-sidedly on consequences of stress [19]. Single intervention studies have been evaluated using this tool [18]. In a cross-section study involving 281 patients the French translation was utilised [17].

Conclusion: With a sufficient test construction it is a good instrument for evaluation studies.

(5) 1991 the *Subjective Tinnitus Severity Scale* (STSS) is devised [3]. The main factor correlates somewhat with depression, anxiety, and the emotion factor of the TQ. Correlation with psychoacoustic tinnitus parameters [3,20] is medium-grade (dB HL $r = 0.41$). The STSS was evaluated in 104 Dutch patients [20]. The scales “emotional distress”, “intrusiveness”, “annoyance” and “cognitive distress” were analysed. In contrast to the THQ and the TRQ no significant correlations was found between the STSS and psychopathological traits [shortened version of Minnesota Multiphasic Personality Inventory MMPI-scores; 17]. The STSS was utilised among others in a predictor study [21] and in a cross-section examination [20]. Normal-value data could not be verified. The graduation-analysis is not valid ($n = 30$). According to results of analysis, the STSS is less useful in the evaluation of intervention studies than the TQ/TF [20].

Conclusion: With reservations useful test instrument.

(6) The *Tinnitus Severity Questionnaire* TSQ [22] displays insufficient test quality of the instrument. Difficulties with tinnitus masking and tinnitus impairment showed good correlations [$r = 0.60; 11$]. Intervention studies using the TSQ (short version with 6 items) were not able to document changes in the items “Quality of Life” and “Concentration Difficulties” [23].

Conclusion: Very unreliable test instrument.

(7) The *Tinnitus Handicap Inventory* THI was developed 1996 [19]. The selection of items is extremely unsatisfactory. Thus, the existing vertigo and hearing loss questionnaires were adopted partially and adapted to tinnitus. A study on item characteristics of the THI, were able to show sufficient reliability for only 12 items [5]! The relationship to the not yet validated THQ displayed correlations of 0.47 to 0.72; [9]. In a study involving 29 patients [4] a high test-retest reliability was found, and a quartile analysis with a sample of only 29 patients (!) was performed. The quartile analysis is not valid. With that, the authors declared their instrument to be robust.

Conclusion: With reservations useful test instrument.

(8) The original British items of the *Tinnitus Questionnaire* (TQ) [6] were painstakingly selected

Table 2 Descriptions of international Tinnitus Questionnaires

| Name of Questionnaire | Ref. | No of Items | Coding of Items | Factor Analysis | Factor Structure | Examined Patients | Cronbach's a | Test-Retest-Reliability | Norms |
|---|-------|-------------|--|--|--|--|--|--|--|
| 1. Tinnitus Stress Test (TST) | 13 | 16 | 4-7 levels | none | Thematic outline, intensity index, impairment, depression | 60 patients [14] | not examined | not examined | none |
| 2. Tinnitus Severity Scale (TSS) | 15 | 15 | 4 levels | none | — | 24 patients | not examined | total: 0.86 interval: 14 days | none |
| 3. Tinnitus Handicap Questionnaire (THQ) | 1 | 27 | scale of 0-100 | oblique | I. effects of tinnitus on social, emotional and physical behaviors II. hearing ability III. patients' view of tinnitus | >500 patients | total test: 0.94 factor: 0.47 0.95 | not examined | percentiles for total & for Factor I to III n = 275 |
| 4. Tinnitus Reaction Questionnaire (TRQ) | 2 | 26 | 5 levels 0 = no / none 5 = nearly always | orthogonal | I. general distress II. interference with work and leisure activities III. severe signs of distress IV. avoidance of activities | >600 patients | total: 0.96 | total: 0.88 | merely clinically suggested |
| 5. Subjective Tinnitus Severity Scale (STSS) | 3 | 16 | dichotomous (yes - no) | orthogonal v. Veen <i>et al.</i> 1998; 4 factors | I. distress intrusion II. cognitive focus III. irritant IV. constancy V. distraction | >500 patients | total: 0.90 | not examined | 3 grades for total n = 30 |
| 6. Tinnitus Severity Questionnaire (TSQ) | 22 | 10 | 5 levels | orthogonal | I. generalized tinnitus severity | >1300 patients | not examined | 0.62-0.79 interval: 18 months | none |
| 7. Tinnitus Handicap Inventory (THI) | 4, 19 | 25 | 3 levels 0 = no; 2 = some-times; 4 = yes | orthogonal | I. functional II. emotional III. catastrophic | 66 patients | total 0.93 factor: 0.68 - 0.87 n = 110 (1996) | n = 29 (4) total: 0.92 interval: 20 days | n = 29 [4] quartiles for total |
| 8. Tinnitus-Questionnaire (TQ) and Tinnitus-Fragebogen (TF) | 6, 7 | 40 | 3 levels 0 = no; 1 = some-times; 2 = yes | orthogonal analyses with step-by-step factor extraction | I. psycholog. distress II. intrusiveness III. hearing difficulties IV. sleep disturbances V. somatic complaints | >900 probands from widely spread analysis sample (Great Britain and FRG) | total: 0.94 factor: 0.78-0.92 n = 93 (GB) n = 138 (FRG) | total: 0.94 Factor: 0.89-0.93 interval: 3 days n = 60 | quartiles for total & for Factor I to V; n = 50 GB; n = 623 multi-center FRG |

Table 3 Appraisal of tinnitus questionnaires

| Psychometrics | TST [13] | TSS [15] | THQ [1] | TRQ [2] | STSS [3] | TSQ [22] | THI [4,19] | TQ/TF [6,7] |
|-------------------------|-------------|-------------|------------|------------|-------------|-------------|---------------|----------------|
| number of items | 16 | 15 | 27 | 26 | 16 | 10 | 25 | 40 |
| item selection | ± | + | ++ | + | + | -- | ± | +++ |
| factorial stability | -- | -- | ++ | ++ | ++ | + | + | +++ |
| internal consistency | -- | -- | +++ | +++ | +++ | ± | +++ | +++ |
| test-retest-reliability | -- | + | +++ | +++ | -- | -- | +++ | +++ |
| convergent validity | -- | -- | ++ | ++ | ++ | -- | ++ | ++ |
| construct validity | + | -- | ++ | ++ | +++ | + | ++ | +++ |
| objectivity | + | +++ | + | ++ | + | +++ | +++ | +++ |
| practicability | ± | ++ | ++ | ++ | + | ++ | + | +++ |
| graduation studies | -- | -- | +++ | + | -- | -- | ± | +++ |
| test-cases | ± | + | + | ++ | ++ | +++ | + | +++ |
| psychometrically robust | - | -- | +++ | +++ | +++ | +++ | + | +++ |
| | no | no | good | good | (good) | weak | (good) | excellent |

[24] and in 1987 further developed in Germany to a *Tinnitus-Fragebogen* (TF) with semantically and linguistically comparable structure and validated on a broad basis [7,25,26,27]. The solution with 5 factors was confirmed (12). The quartile analysis was based on data from 600 patients from different institutions all over Germany. After numerous developmental steps, TF and TQ have equivalent structures and are therefore suited for transcultural analyses. With regard to their acceptance in the scientific community and to the publication as manuals, both instruments are the most valid ones in international research. For the German version, evaluation software is available, offering a supreme level of objectivity and practicality [7].

Conclusion: Excellent, broad-spectrum tinnitus complaint questionnaire.

Studies with the TF

In Table 4, we have listed the results of several research groups as found in studies using the TF as an instrument to evaluate therapeutic effects in chronic tinnitus. Detailed information is to be found in the cited literature. We have listed the relevant facts in the table as necessary for a basic overview.

Discussion and conclusion

Scientific evaluation and research of tinnitus severity in certain patients and patient groups is a task

which requires a professional approach. If it is not possible to raise the measurement of therapeutic successes from the range of individual estimation or mere guesswork, many of the efforts to formulate indications for treatment remain weak in effect, networking between research groups is highly subject to shortcomings, and the patients suffering from tinnitus will fail to be understood in their distress. Tinnitus questionnaires are important diagnostic instruments for assessing various complaints from different fields of life in connection with tinnitus. By distribution and growing acceptance of valid instruments in science, in medical appraisals, and in certain therapeutic areas, the problems associated with tinnitus will become clearer, and we will be able to guide patients to individually suitable therapeutic options with more efficiency [34].

The treatment results evaluated here with the TF, involving highly selected samples make it difficult to summarise and judge the studies comparatively. For patients with mild tinnitus, less frequent therapeutic sessions are sufficient (Counseling, TRT or TCT). If symptoms suggest a high tinnitus burden or impairment, further anamnestic and psychological findings must be collected to gauge whether social, job-related, or family-related problems, or psychiatric factors affect the tinnitus impairment and thus the outcome of treatment. For this patients multimodal treatments are indicated (inpatients).

Table 4 Studies involving patients with chronic tinnitus, evaluation with the Tinnitus-Fragebogen TF [7]; references in parentheses are available from the authors (N = sample size; form: inpat. = inpatients; group = group-design; indiv. = individual-design; T1: prior; T2: post; \pm TF: Difference in TF global-score; sign. = $p < 0.05$ and smaller; NG = Noise Generator; TRT = Tinnitus Retraining Therapy; TCT = Tinnitus Coping Therapy)

| | Studies | N | form | T1 | T2 | \pm TF | week | sign. | Comments |
|-----------------------|--|-----|--------|------------------|------------------|----------|--------|-------|---|
| waiting for therapy | Kröner-Herwig <i>et al.</i> 1997 Düsseldorf [28] | 20 | indiv. | 38,7 \pm 13 | 35,9 \pm 14 | -3,2 | 30 | n.s. | |
| waiting for therapy | Goebel <i>et al.</i> 1999, Prien [29] | 27 | indiv. | 56,1 \pm 9 | 57,1 \pm 8 | 1,0 | 26 | n.s. | Unimpaired hearing |
| NGT | Goebel <i>et al.</i> 1999, Prien [29] | 16 | indiv. | 55,7 \pm 9 | 55,3 \pm 13 | -0,4 | 16 | n.s. | Selection TF >40 Noise generator |
| Counseling | Kröner-Herwig 1997, Düsseldorf [28] | 16 | group | 36,3 \pm 14 | 28 \pm 15 | -8,3 | 8 | sign. | 1 \times T1 & T2 |
| Counseling | Haerkötter & Hiller 1999, Mainz [30] | 11 | group | 27,3 \pm 7 | 12,7 \pm 7 | -14,6 | 4 | sign. | Selection TF >40 |
| TRT | Goebel <i>et al.</i> 1999, Prien [29] | 10 | group | 47,2 \pm 9 | 39,7 \pm 12 | -7,5 | 16 | sign. | Selection TF >40 noise generator |
| TRT | Biesinger <i>et al.</i> 1997, Traunstein [31] | 42 | indiv. | 56,4 \pm | 42,3 \pm | -14,2 | 52 | sign. | Selection TF >52 noise generator |
| TRT | Haerkötter & Hiller 1999, Mainz [30] | 16 | group | 34,9 \pm 11 | 17,2 \pm 8 | -17,7 | 4 | sign. | Selection TF >40 noise generator |
| TCT | Kröner-Herwig 1997, Düsseldorf [28] | 43 | group | 35,6 \pm 14 | 23,6 \pm 14 | -12 | 11 | sign. | Multimodal 1 \times 120 min./week |
| TCT | Rübler 1996, Trier [7] | 20 | group | 44,6 \pm 15 | 30,8 \pm 16 | -13,8 | 10 | sign. | Multimodal 2 \times 90 min / week; |
| TCT | Haerkötter & Hiller 1999, Mainz [30] | 8 | group | 51,2 \pm 5 | 33,9 \pm 8 | -17,3 | 10 | sign. | Selection TF >40 |
| TCT | Goebel <i>et al.</i> 1999, Prien, [29] | 7 | group | 50,8 \pm 15 | 40,7 \pm 12 | -10,1 | 16 | sign. | Selection TF >40 Unimpaired hearing |
| cognitive-behavioural | Rabaioli & Goebel 1999 [7] | 14 | indiv. | 41,5 \pm 12 | 26,2 \pm 17 | 15,3 | 24-100 | sign. | Psychiatric co-morbidity +++ |
| cognitive-behavioural | Goebel <i>et al.</i> 1996, Prien [32] | 138 | inpat. | 51,2 \pm 18 | 46,4 \pm 17 | -7,8 | 8 | sign. | Psychiatric co-morbidity +++ |
| cognitive-behavioural | Schätz 1999, Prien | 36 | inpat. | 48,3 | 38,2 | -10.1 | 8 | sign. | Psychiatric co-morbidity +++ |
| "Tinnicur" | Gronholz 1996, Düsseldorf [7] | 48 | indiv. | 30,1 \pm 17 | 22,6 \pm 12 | -7,5 | 24 | sign. | Daily 2 \times 30 min. audio-tape Musik by Mozart |
| Placebo "Tinnicur" | Gronholz 1996, Düsseldorf [7] | 47 | indiv. | 34,7 \pm 12 | 26,4 \pm 17 | -8,3 | 24 | sign. | Daily 2 \times 30 min. audio-tape Musik by Mozart |
| Relaxation-musik | Kröner-Herwig 1997, Düsseldorf [28] | 16 | indiv. | 42,9 \pm 13 | 31,4 \pm 10 | -11,5 | 11 | sign. | Daily 1 \times 20 min. relax.-audio-tape |
| Autogenes Training | Waszak 1996, Düsseldorf [7] | 14 | group | 38 \pm 15 | 29,5 \pm 13 | -8,5 | 5 | sign. | 2 \times 90 min./week Selection severe tinnitus |
| Yoga | Kröner-Herwig 1997, Düsseldorf [28] | 25 | group | 42,9 \pm 17 | 34,6 \pm 17 | -8,3 | 8 | sign. | 2 \times 90 min./week |
| Medicine | Laser & Ginko [33] | 47 | indiv. | 50,7 \pm 17 | 48,7 \pm 18 | -2 | 16 | n.s. | Blind study |
| Medicine | Placebo-Laser & Placebo-Ginkgo [33] | 36 | indiv. | 48,9 \pm 21 | 43,3 \pm 20 | -5,5 | 16 | n.s. | Blind study |
| follow up | Rübler 1996, Trier [7] | 20 | | 30,8 \pm 16 | 31,8 \pm 17 | 1,0 | 12 | sign. | After TCT |
| follow up | Kröner-Herwig 1997, Düsseldorf [28] | 43 | | 23,6 +14 | 23,2 +15 | -0,4 | 24 | n.s. | After TCT |
| follow up | Kröner-Herwig 1995, Düsseldorf [28] | 25 | | 34,6 \pm 17 | 33,6 \pm 14 | -1,3 | 24 | n.s. | After Yoga |
| follow up | Kröner-Herwig 1997, Düsseldorf [28] | 16 | | 28 \pm 15 | 25,9 \pm 16 | -2,1 | 24 | n.s. | After Counseling |
| follow up | Goebel <i>et al.</i> 1996, Prien [32] | 31 | | 46,4 \pm 17 | 46,6 \pm 15 | 0,2 | 52 | n.s. | After clinic; psychiatric co-morbidity +++ |
| follow up | Biesinger <i>et al.</i> 1997, Traunstein [31] | 42 | indiv. | 43,3 \pm | 42,3 \pm | -1,0 | 52 | n.s. | After TRT noise generator |
| follow up | Schätz <i>et al.</i> 1999, Traunstein | 12 | | 31,4 \pm 16 | 25,6 \pm 18 | -5,8 | 104 | n.s. | After ENT; psychiatric co-morbidity none |
| follow up | Schätz <i>et al.</i> 1999, Prien | 36 | | 38,2 \pm 19 | 42,6 \pm 22 | 4,4 | 104 | n.s. | After clinic; psychiatric co-morbidity +++ |

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Timing of intervention and the emotional coping with tinnitus

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The focus of this paper will be the interaction between the timing of the rehabilitative interventions by professional health workers and the patient's process of coming to terms with tinnitus. This timing appears to influence the effectiveness of the rehabilitative efforts.

Introduction

Coming to terms with the presence of the tinnitus itself, the related emotional disturbance and the resulting effects on one's functioning in family life, work and leisure activities can be a laborious process for the patient. Wilson *et al.* [1] conclude: 'The psychological presentation of patients with tinnitus is often quite complex, involving depression, anxiety and anger'. The important role of psychological aspects in the rehabilitation is emphasized by Jastreboff and Hazell [2] as they state counselling to be an integral part of their Tinnitus Retraining Therapy. Sheldrake *et al.* [3] describe that in this retraining therapy habituation of the reaction, the emotional responses, precedes the habituation of perception.

This suggests a sequence of professional procedures, a timing of different types of intervention. To begin with the professional worker has to assess the issues concerning the emotional coping of the patient which have to be dealt with. This assessment needs to meet the patient's process of coming to terms with his tinnitus and its consequences.

However, a theory or model about this process tailored to patients with tinnitus seems not to be available. We therefore have to look for related theories.

Freud for example, has taught us about grief therapy. He states that 'Trauerarbeit', 'grief work' has to be done. He emphasizes the necessity to acknowledge and work through the emotional pain. 'To work through' suggests an active process; efforts are required.

A more recent well-known model has been presented by Kübler-Ross [4] with regard to the process of accepting serious illness and forthcoming

death. She describes five stages patients have to work through: denial, rage and anger, bargaining, depression and acceptance. Horowitz [5] describes a model of consecutive states of stress responses in consequence of a serious life event.

Although some elements of these models can be recognized in the process of emotional coping of our tinnitus patients, these models are not fully applicable. They are developed for other categories of shocked people and assume too much a predictable clearly ordered course.

Perhaps a more proper frame of reference might be the study of severe loss. Chronic tinnitus might be perceived as the loss of silence. The intrusiveness of the unwanted sound(s) can be threatening and can more generally be felt as the loss of physical integrity. Thus for severely distressed patients tinnitus can mean a confrontation with a variety of loss experiences. The Dutch psychologist De Mönnink [6,7] worked out a model, based on descriptions by Worden [8], which gives a well-structured description for the process of coming to terms with loss experiences in a wider sense. The model deals with the types of loss which are to be characterized as important life events, mobilizing strong feelings of helplessness and thereby disrupting one's life.

A study of loss

In his study of loss De Mönnink distinguishes six elements in man's existence: the body, the psyche, relationships, school/work, parenthood, and house and home. In each of these areas loss experiences can take place. Not the facts of the loss determinate their range, but rather their meaning for the person concerned, the individual reactions and their consequences. To analyse the impact of loss experiences De Mönnink describes several dimensions: the existential dimension, the individual dimension, the dimension of the family as a system, the social network, the communicative dimension, the dimen-

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sion of the course of life, the cultural dimension and the professional dimension.

The model gives a frame of reference to analyse the patient's process of coming to terms with his loss experiences. The issues identified are called the tasks of emotional coping the patient has to complete. They provide the professional worker with the basis for his treatment.

Without losing sight of the other dimensions mentioned by De Mönink, the existential and individual dimension seem to be specially useful as far as tinnitus is concerned. These dimensions will now be discussed.

The *existential dimension* refers to the subjective meaning of the loss and its disturbing effects on one's sense of self. It means losing firm ground, having nothing to go by. Four corner stones of existence can be threatened.

- 1 The *loss of control*: For tinnitus patients this means: Whatever I do, it is of no use! The tinnitus drives me mad! People are losing their grip on their selves and their lives.
- 2 A *sense of lowered self-esteem*: Failing attempts to cope with the problem can lead to a sense of lowered self-esteem. The experienced inability may lead to a damaged self-image, sometimes felt as a loss of face. When this happens, personal efficacy is challenged.
- 3 The *sense of justice*, fundamental life values are at stake: Why me?, I do not deserve this!
- 4 *Prospects* might be hampered. The direction in life has become uncertain. Does the tinnitus also mean that I have to give up future plans, objectives, activities I like or even my work?

The *individual dimension* concerns possible individual reactions, relating to three process components: resistance, leave-taking and accommodation. These modes of reacting can occur again and again, all the time relating to another painful aspect of the essential loss experience. They do not take a predictable clearly ordered course.

The three process components will be described as follows.

Resistance is a defence mechanism that may be necessary to keep going. The loss and its consequences may be so disrupting that one can not accept its reality. One sees in this context that tinnitus patients do not accept there is no medical treatment and continue to look for another doctor or an alternative treatment. This searching behaviour also has a functional side. It means having done everything one could. You need not blame yourself.

Taking leave of the 'natural' rest in your head is the primary loss when the tinnitus appears to be chronic. And there are also secondary losses. Tinnitus usually is tiring and less energy will be left. So it can mean taking leave of the energetic person one was, of the lifestyle one was used to. Also an opposite reaction is possible. Rest can mean confrontation with the noise(s), which leads to hyperactivity. Then the condition of rest is lost. And circumstances, activities might exacerbate the annoyance. For

example this can mean taking leave of (social) activities, of attending concerts, leisure activities, of one's career or even one's job. Often it means losing friends. Leave-taking is a process characterized by emotional, behavioural and cognitive reactions and sometimes somatic complaints. Giving way to the emotional pain, coping with depressive reactions, anxiety, loss of initiative, social isolation, withdrawal behaviour and disturbing thoughts might be tasks to accomplish. It also means giving up the demand for a medical solution. Only when this is overcome, an important condition will be fulfilled to create susceptibility to tinnitus rehabilitation.

Accommodation means adapting to the new situation. This is not a state of passive resignation, but rather an emotionally and cognitively integrated sense of acceptance. If reality can not be changed, which is the case with tinnitus, one can try and change one's perceptions, ideas and feelings. The reality of tinnitus and its consequences might be assimilated and relocated in one's life. This means learning to alter the reactions to tinnitus, to develop effective coping strategies and a lifestyle adjusted to the new situation. The control over one's feelings and functioning will be required as well as the sense of self-esteem. The sense of justice can be reformulated, although the question 'Why me?' might not be ultimately answered. The annoyance of the tinnitus will become manageable, although one does not always succeed as well as one should wish. Life will not be like it was before, but it is worth finding out what can be regained and to discover that life can be enjoyed again.

For the professional worker these processes relating to the existential and individual dimension mean that they are of help to make an inventory of the issues that dominate in the patient's process of coming to terms with his loss experiences. The predominant issue, that means the issue that mostly bothers the patient in the here-and-now situation, should be the focus of counselling. When that actually-felt problem is recognized the patient will then be most receptive to change his cognitions, feelings and behaviour. Both Worden and De Mönink emphasize the importance of accordingly timing the issues to be discussed.

Two case reports will illustrate how the model can be of use.

Case reports

The case reports will illustrate not only how the model can be of use as a frame of reference to assess the dominating aspects of the process of accepting the tinnitus but also which tasks have to be accomplished according to the existential and individual dimension. The case reports also illustrate the importance of timing and its effect on the rehabilitative outcome.

Case 1

Mrs K, 56 years old, married, 4 children, two sons of 16 and 18 years old still living at home. She calls

herself an 'ordinary housewife'. She also has a part-time cleaning job and serves in a staff canteen. She was a cheerful, nervous and active person. She loved caring for people and was involved in a lot of (social) activities.

The onset of tinnitus happened four years ago. She continually hears two noises: humming and rustling. The annoyance is fluctuating, worst in the weekends, increasing in the last two years. She has a binaural moderate hearing loss of 60 dB for the right ear and 50 dB for the left ear.

She saw two ENT-specialists. The first one advised a hearing aid. She tried one, but found the tinnitus was still there. The second specialist reassured her that a hearing aid would help and that she had to learn to live with her tinnitus. She was referred to an Audiological Centre. There she got the advice to change her lifestyle: less busy, more rest. She tried to. But meanwhile she worried about the activities still to be done. The hearing aid offered did not affect her tinnitus. Disappointed she stopped the rehabilitation and started to look for alternative therapies.

Meanwhile she did not manage to continue her work and she reported sick. Then a friend gave her the advice to go to a university hospital for a second opinion. So she came to our hospital and was referred to the tinnitus team. On the ground of her case history we learned that providing a hearing aid would be an unsuitable starting point. To find out what would be a more appropriate start, she was referred to a psychosocial intake.

Main themes in this intake appeared to be: she was losing her cheerful personality, she had lost the grip on her life and was afraid to lose her job. During sleepless nights she thought: Why me? She could not bear the tinnitus anymore; something had to be done!

As resistance to accept the reality of the tinnitus and a sense of loss of control predominated, these were the starting points. In the subsequent counselling sessions she gave way to her grief and was going to accept the tinnitus. She made the transition from the medical model (getting rid of) to the rehabilitation model (learning to live with). In parallel a relaxation training was started with additional desensitization as described by Hallam [9]. To regain her sense of control she had to take leave of her usual lifestyle, of certain activities and of the people involved. She also had to take leave of the very caring person she was. Through assertiveness training she learned to set limits. And she succeeded: she regained her sense of control and learned to get more grip on the annoyance with her tinnitus.

Then we discussed trying a hearing aid again. She now was quite surprised to discover how useful that was for better hearing. Communication was less tiring, which affected the annoyance with her tinnitus in a positive sense.

The timing of offering the hearing aid turned out to be essential for its effect. First she had to deal

with the process of coming to terms with her tinnitus. And also within the psychosocial treatment to facilitate this process, a proper timing for dealing with the several issues had to be achieved. Next to loss of her grip on life and of her identity as a cheerful and caring woman, her sleeping problem, her despair and her fears, predominated her resistance and her loss of control. So first she had to work through her resistance and to regain her sense of control. After accomplishing those tasks, and adjusting her lifestyle she was ready to give the previously rejected hearing aid a new chance.

Case 2

Mr P., 47 years old, living together with his girlfriend, no children. He had been a seaman. After several outbursts of anger and suffering from severe headaches he had been declared unfit for work. Two years ago he started to suffer from tinnitus. He heard bells, rattles, creaking and what he called Martians (men of the planet of Mars). He had problems with sleeping and concentration. He became very depressed and got problems in daily and social functioning. He isolated himself. Since the onset of tinnitus the relation with his girlfriend became more and more disturbed. In social situations he easily got very irritated or even furious.

As a seaman he had consulted doctors in Australia, England and the USA. They did not free him from his tinnitus. Twice he attempted suicide. Back in the Netherlands he had been to an ENT-specialist and neurologist. His medical officer referred him to a psychiatrist because of the Martians he heard and his fits of rage. The psychiatrist was consulted and gave him anti-psychotic and later on anti-depressive medication. These did not affect his tinnitus. Finally he went to an Audiological Centre. The clinical audiologist explained about the noises and Mr P. felt at last understood. However, the prescribed tinnitus masker and the lifestyle-advice given did not work. A tinnitus masker only meant another added noise. And changing his lifestyle was not acceptable. Activities like motorbike riding, fanatically jogging and working with his computer worsened the annoyance of his tinnitus. But slowing down or even giving up these activities he always loved would mean capitulating to the tinnitus. No, he would fight and win. The clinical audiologist prescribed a psychosocial treatment.

As Mr P. related his story he wondered repeatedly why this suffering happened to him, a man who was so keen on silence? This was highly unfair! Angrily he stated that talking was useless. He only wanted to get rid of his tinnitus. But how? We decided to fall in with his resistance and subsequent searching behaviour. We discussed his visits to doctors and alternative treatments and looked for other ways. He decided to visit a monastery.

Then we explored the Martians. He did not really hear voices, but just a lisp as Martians do in science fiction films. We relabelled the Martians lisp noises.

He also decided to start with reincarnation therapy. Meanwhile his anger grew: nothing resulted in success.

Then his disturbed sense of justice became all-important. We discussed his efforts to live as a good man, although he often failed. We discussed his feelings of guilt and shame about some serious failures. He also visited a clergyman. A real answer seemed not to be available. One had to accept. His anger diminished.

As he had been a seaman we discussed in images of a seaman's life that he, being the captain, had to decide on the course: getting rid of his tinnitus or accepting it as a reality and integrate it into his life. His resistance rose again. We discussed again his attempts to get rid of the tinnitus and its results. This seemed to be a course without perspectives. He got angry and sad. We gave way to these feelings and discussed the meaning of rest and silence with him. He started to take leave of the rest in his head as long as no treatment was available and directed his course to trying to live with his noises. He realized that overcoming the tinnitus did not mean to fight against it, but could mean to keep it in control. He was not willing to analyse which factors influenced the annoyance of his tinnitus by diary-registration. But we found out that lately the annoyance had fewer high peaks. He noticed he was getting less involved in quarrels and irritating events, being less easily angry and irritated. He also was brooding less and he slept a bit better. He understood the annoyance of the tinnitus could be influenced by controlling his feelings and by controlling his levels of arousal. It was amazing how rapidly he started to develop strategies to control his level of arousal and to change his lifestyle according to the earlier suggestions of the clinical audiologist. He also directed his attention to rest and relaxation. The annoyance of the tinnitus decreased. However, his searching behaviour continued. He found a 'healing therapist', but now to enhance his relaxation. He ended the therapy by stating that the tinnitus now belonged to him.

Referring to the study of loss in the beginning of the treatment, his resistance dominated, according to the individual dimension. Although we expressed our doubts, we went along with his wishes. The next predominant issue was, according to the existential dimension, the question: Why me?, the disturbed sense of justice. After working through this issue he had to succeed in accepting his tinnitus as a reality, to take leave of the rest in his head, a process which again activated a lot of resistance. If these tasks of coming to terms with his tinnitus had been neglected, the turning point from the medical to the rehabilitative model would never have been achieved. The proper advices of the clinical audiologist to change his lifestyle could only be acted upon after reaching that turning point. The timing of the different issues to be discussed, following the patient according to the predominant character they appeared to have for him at the time, seemed to be crucial for the effectiveness of the different inter-

ventions and the final accommodation to the tinnitus in his life.

Conclusions

The model of De Mönink provides a structure by describing tasks in the process of coming to terms with a tinnitus-dominated life. The model can be of help in identifying aspects of the emotional coping that might block an effective progress in the rehabilitation. Thus it is of diagnostic value.

In the literature as well as in accordance with clinical experience the importance of timing for the different interventions is crucial.

As a result two points seem of great importance.

At first the necessary transition of the patient's attitude from being directed to the medical model (getting rid of the tinnitus) to being focused on the rehabilitation model (learning to live with). A confirmation of this clinical experience is found by Vesterager [10] in his study concerning an evaluation of a tinnitus management program. If this transition, giving up the demand for a medical solution and accepting the reality of the tinnitus, is neglected, rehabilitative interventions will be judged by the extent to which they take away the tinnitus. That means they hardly have any chance, although they might be suitable in a later phase.

The second point concerns the timing of the several parts of the rehabilitative interventions. The process of emotionally coping, accepting the tinnitus as a fact in one's life has to attain a certain progress before the actual rehabilitation can start. To express it in terms of the study of loss: certain tasks of coming to terms with the tinnitus and secondary losses do have to be accomplished before a certain tolerance to the tinnitus, as written by Hallam *et al.* [11] in a habituation model, is going to take place. Only then technical procedures and psychotherapeutic interventions of learning how to live with tinnitus might be successful. If this timing is neglected, rehabilitative efforts may be ineffective and may mean a lot of wasted energy and time.

Assessing the varying major tasks in coming to terms with tinnitus and assessing their relative importance, can give a good indication of determining the sequence of the different steps in rehabilitation. Next to its diagnostic value the model can be especially useful in the timing of rehabilitative interventions.

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Results of an outpatient cognitive-behavioral group treatment for chronic tinnitus

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An 11-session cognitive-behavioral group treatment (outpatient) for chronic tinnitus was developed and evaluated in a randomized group design. The tinnitus coping training (TCT) was compared to a minimal contact intervention (MCI, 2 sessions with education and self-help instructions) and a waiting-list control (WC). For all three groups a broad range of variables was registered at baseline and at post-treatment period. The TCT group was also evaluated at a 6-months follow-up. TCT demonstrated good efficacy regarding reduction of disability and annoyance due to tinnitus, and a distinct improvement of coping. Effect sizes of pre-post changes in the TCT group were medium to high in contrast to low effect sizes in the control group. MCI effect scores lay in-between.

Introduction

Clinical observations in Germany suggest that tinnitus is a growing health problem. Medical treatment of tinnitus has not made much progress in recent years and the elimination of tinnitus, especially of chronic tinnitus (CT), by medical means remains as yet out of reach. The main objective of psychological interventions in CT is the reduction of disability and annoyance due to tinnitus and thereby the improvement of quality of life. It has been shown that disability is not determined by the audiological characteristics of tinnitus, but rather by psychological processing of the inner noise [1]. Several studies on psychological interventions [2,3,4,5] have produced encouraging results.

The aim of our study was to develop and evaluate a cost-effective group training (outpatient) within a cognitive-behavioral framework. We intended to manualize the training in order to make it available for health care services in a standardized format [6]. Furthermore the treatment was to be compared to a minimal contact intervention employing an educational self-help approach.

Methods

A randomized group design was used to compare the group training (Tinnitus Coping Training, TCT) and the minimal contact intervention (MCI) with a self-monitoring waiting-list control group (WC). TCT comprised 11 sessions of 90–120 minute duration and was administered to groups of 5–8 patients. A total of 43 patients were treated and evaluated at baseline (pre-treatment), immediately after training (post-treatment) and at 6-months follow-up (follow-up).

The treatment protocol included the following intervention modules [6]:

- education on the physiological and psychological factors playing a role in tinnitus;
- relaxation exercises;
- identification of cognitive processing (e.g. automatic thoughts regarding tinnitus, worrying, catastrophizing) and emotional responses (e.g. depression, anger, helplessness to tinnitus);
- modification of cognitions and emotional responses;
- use of attention distraction strategies;
- transforming tinnitus through imagery;
- analysis of avoidance behavior and areas of disability;
- modification of avoidance behavior and the use of cognitive-behavioral coping techniques;
- exploration of attitudes towards illness and health and their influence on tinnitus;

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- coping with tinnitus after therapy (coping with relapse).

Treatment was administered by 4 post-graduate clinical psychologists (2 women, 2 men).

The MCI consisted of two group sessions which were attended by all Ss assigned to this treatment condition (originally $n = 20$). In session 1 patients were educated regarding physiological and psychological processes involved in tinnitus perception, and cognitive-emotional processing. The biopsychological model conveyed in this session illustrates the usefulness of self-help strategies (e.g. attentional distraction, sound enrichment, etc.) in effectively reducing annoyance due to tinnitus. The use of these strategies was encouraged. In a second session 4 weeks later successful use of these strategies or problems that arose using them were discussed with the patients. For the MCI and WC groups no follow-up was conducted, since members of these groups were given the opportunity to join TCT after the post-therapy assessment period, if they wished to (second phase of treatment).

Standardized instruments were used in the evaluation of outcome:

- a two-week tinnitus diary (assessing different tinnitus variables: subjective loudness, hrs. of not being aware of tinnitus, subjective control) was completed at baseline and the subsequent assessment periods;
- the Tinnitus Questionnaire (German version of the questionnaire developed by Hallam and collaborators [7]);
- the Tinnitus Disability Index (adapted version of the Pain Disability Index);
- a tinnitus coping questionnaire (German test)
- the symptom checklist for psychopathology (SCL 90-R, German version);
- a depression questionnaire (CES-D, adapted German version);
- the patient's ratings of changes due to therapy (relating to tinnitus and general well-being).

Audiological data (masking level, sensation level) are not reported here, since they are generally not sensitive to therapy and are furthermore not relevant to disability or suffering.

Information on the research project was published in various local newspapers as a manner of recruiting patients. 522 patients voiced desire to participate in the study. Ss could enter the study, if they had been afflicted with tinnitus for at least 6 months, were between 18–65 yrs. of age, and rated their annoyance due to tinnitus in the middle range or higher on each of nine 5-point scales measuring different aspects of disability (e.g. regarding concentration, affective state).

Patients were excluded from the study if an organic diagnosis for tinnitus was present or probable (Morbus Menière, tumor etc.), if tinnitus was not the main health problem, if hearing loss was so advanced that it would complicate communication in groups, or if other treatments for tinnitus were pending. After this selection procedure 56 patients

were randomly assigned to TCT, 20 to WC and MCI each. A further 90 patients of the total 257 fulfilling the inclusion criteria were assigned to treatment conditions not described here. Due to the limited treatment capacities the remaining 81 patients could not be offered treatment.

Three TCT patients were excluded from evaluation because of missing data, 10 further patients dropped out of the study for various reasons. Also 4 patients of MCI dropped out.

Patients remaining in the study were 46 years old on the average (range 19–64 yrs.), 52% were female. About 48% had completed higher education. Average duration of tinnitus was 57 months (range 6–206 months).

Results

The statistical comparison of TCT and WC by means of multivariate 2-factorial (group/period) analyses of variance reveals a significantly higher improvement rate in TCT in 5 of the 6 areas of assessment (diary variables, coping variables, disability variables, improvement ratings regarding tinnitus and well-being; see Table 1).

Table 1 Results of multivariate 2-factorial analyses of variance (interaction group = period) and mean intergroup effects sizes

| dependant variables | mean ES | interaction (G X P) |
|---------------------|---------|---------------------|
| diary variables | 0.63 | $p = 0.0001$ |
| coping variables | 1.21 | $p = 0.000$ |
| disability | 0.85 | $p = 0.004$ |
| subjective change: | | |
| •tinnitus variables | 0.65 | $p = 0.001$ |
| •well being | 0.65 | $p = 0.002$ |
| mean | 0.86 | |

The Tinnitus Questionnaire score, our main outcome score, demonstrated a marked and stable improvement (Figure 1). It is, however, noteworthy that reduction of annoyance is also evident in MCI, even the waiting-list control shows a small decrease. The outcome variables relating to psychopathology (SCL 90-R, CES-D) did not evidence a significant change after therapy; a result which can be easily explained by the fact that the scores did not deviate significantly from the norm at baseline (percentile score 50–64).

Stability of improvement was tested by comparing post to follow-up scores (dependent t-tests). Nearly all scores remained unchanged except for use of relaxation as a coping strategy, which decreased significantly at follow-up as did subjective control. Both variables, however, remained well

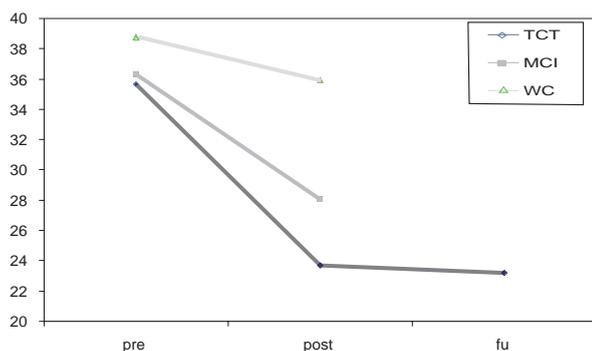


Figure 1 Sum scores of the Tinnitus Questionnaire for all three treatment conditions at different time periods

above baseline level. The awareness of tinnitus at follow-up was significantly lower than the post-therapy level. Differences in outcome between MCI and TCT did not reach a significant level except for the coping strategies. Ss treated with TCT reported more frequent utilization of adaptive strategies than patients of the MCI group (multivariate analyses of the variance).

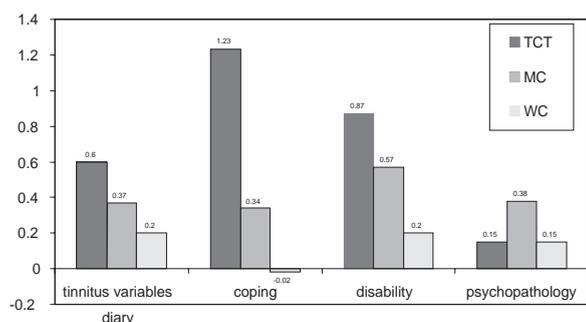


Figure 2 Mean intragroup effect sizes (pre-post) for groups of variables

Intra-group effect sizes were calculated for all groups; (see Figure 2). They demonstrate that in every case the highest effects are found in TCT, the lowest in WC, while MCI effects lie between the two (ignoring the psychopathology scores).

It was of further interest to establish which variables could predict improvement in TCT, as defined by reduction in disability due to tinnitus (TF). Changes in the use of coping strategies at post-treatment were entered into a regression analysis with the criterion variable 'change in disability'. Catastrophizing and self-encouragement explained a total of 38% of the variance. Relaxation, distraction and subjective control were not identified as significant predictors.

Discussion and conclusion

The study reveals the overall good efficacy of TCT. TCT led to a reduction of every-day subjective loudness and awareness of tinnitus, as well as an increase in the feeling of control over tinnitus, all as assessed by a two-week diary. TCT improves cop-

ing by reducing catastrophizing, reinforcing the use of distraction and relaxation, and enhancing self-encouragement. The regression analysis demonstrates that coping can be seen as mediator of improvement, defined as a decrease in disability and annoyance as measured by the Tinnitus Questionnaire. These findings emphasize the special role of catastrophizing and self-encouragement in the process of reducing the negative impact of tinnitus, whereas relaxation, distraction, and self-control beliefs do not correlate with a decrease of disability. The use of relaxation decreased at follow-up relative to post-treatment as did self-efficacy beliefs, both, however, without any negative consequence for improvement.

Most patients share the conviction that these positive changes regarding tinnitus coping and annoyance are the result of treatment.

General positive changes, not directly involving tinnitus, were also found: improvement of general stress coping abilities, more positive mood, and improvement of physical well-being. The level of activity, in contrast, was not influenced.

This study emphasizes the long-term stability of treatment effects (at least up to 6 months). Furthermore TCT is shown to be a cost-effective treatment, since, as an outpatient group training therapy, it is rather inexpensive (approximately 200 Euros per patient).

Nevertheless the results suggest that minimal intervention strategies like education and self-help instructions can be effective in some patients and these may not need any further treatment. Thus educational strategies should precede cognitive-behavioral therapy and their efficacy should be evaluated for each individual participant in order to determine whether a group training is necessary for the person or not. It is also very likely that outpatient TCT can replace inpatient treatment in psychosomatic clinics for a considerable number of patients. The authors believe that the results of the study presented here merit confidence regarding their external validity since a replication attempt by a different research group led to very similar findings regarding efficacy [8].

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Association between tinnitus and the diagnostic concept of somatoform disorders

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Two studies are reported that examine the relationship between tinnitus and the diagnostic concept of somatoform disorders. These disorders are defined by physical symptoms which are not, or not fully accounted for by physical disease or general medical conditions. The first investigation, an international study of the World Health Organization (WHO), showed that the prevalence of medically unclear tinnitus was increased among patients who met the criteria of a somatoform disorder according to ICD-10. The second study differentiated between highly distressed (decompensated) and emotionally stable (compensated) patients with chronic tinnitus. Decompensated patients not only showed more comorbidity with somatoform and other mental disorders, but were also characterised by a higher level of dysfunctional beliefs and attitudes which are typical for somatoform disorders. It is concluded that although tinnitus and somatoform disorders are closely associated, further studies are needed to clarify whether psychological distress related to tinnitus underlies similar mechanisms as emotional and cognitive processes found in somatoform disorders.

Introduction

Tinnitus is a physical symptom that can be linked to various medical and pathophysiological conditions. It has been shown that cochlear dysfunctions such as those associated with sudden hearing loss, Menière's disease, noise trauma or hearing loss play a crucial role in most patients presenting with acute tinnitus [1]. However, there are still many cases in which tinnitus is experienced despite negative findings in all relevant medical and audiological tests. The term 'idiopathic tinnitus' is then used by some authors [2], although benign physiological deficits may be present which can not be detected by existing diagnostic methods. Furthermore, as different hypotheses have been proposed about the exact nature of cochlear dysfunctions and their role as underlying pathophysiological processes of tinnitus, more scientific studies are needed to clarify these mechanisms. It has also been suggested that psychological factors such as attention and the subjective interpretation of the tinnitus symptom may contribute to development of distress and disability

[3,4]. Therefore, due to these complex interactions and the limitations of our current knowledge, tinnitus remains medically unexplained in many cases seen in everyday's clinical practice.

The term 'medically unexplained' is highly characteristic also for the group of the so-called somatoform disorders. These are defined as diagnostic categories by the tenth International Classification of Diseases, ICD-10 [5], and the fourth edition of the American Diagnostic and Statistical Manual of Mental Disorders, DSM-IV [6]. Somatoform symptoms and disorders are characterised by bodily complaints in the absence of demonstrable or sufficient organ pathology. A somatoform disorder is to be diagnosed if patients suffer to a clinically relevant degree from their symptoms or are impaired in occupational, social or other important areas of functioning. Although tinnitus is not included in the current lists of somatoform symptoms, the similarities and possible interrelationships between both concepts need to be investigated.

We therefore present data from two independent studies in which tinnitus as well as somatoform disorders were assessed. Study 1 is an international study launched by the World Health Organization (WHO) to evaluate medically unexplained physical symptoms in patients treated in the primary care and general medical setting. Study 2 was conducted

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in the Roseneck Centre of Behavioural Medicine in Prien, Germany, and in an ear, nose and throat practice in Southern Germany with the aim of describing the psychopathological profile and associated characteristics of patients suffering from both mild (compensated) and severe (decompensated) forms of chronic tinnitus. In both studies, structured and reliable interviews were used to assess tinnitus as well as somatoform symptoms as defined by ICD-10 or DSM-IV.

Methods

Study 1

In 1993, the WHO initiated an international project on somatoform disorders which aimed at exploring nosological, methodological, epidemiological and cross-cultural aspects of medically unexplained symptoms in different cultures [7–9]. It included a study of rates and culture-specific characteristics of somatoform disorders. Centres in the following 11 countries participated: Brazil, Bulgaria, China, Estonia, Germany, India, Italy, Japan, United Kingdom, USA and Zimbabwe. A large body of data was collected on more than 60 symptoms for which there was no medical explanation. One of these symptoms was ‘ringing or buzzing in ears or head’ (tinnitus).

Patients came from the routine clinical care of each centre and were selected on a random basis. They were first screened for medically unclear bodily complaints. A more thorough examination was made if there was evidence of at least three clinically relevant somatoform symptoms during the previous six months or at least one symptom lasting for a month or more. The Somatoform Disorders Schedule [10], a fully structured interview for diagnoses according to ICD-10 and DSM-IV criteria, was then administered. The interview questions are fully spelt out and followed by structured probe questions to assess clinical significance of the complaints reported by the patient. The interview also rules out causal physical illness, injury or other medical condition, or associated use of alcohol, drugs or medication. Subjects with positive somatoform symptoms were additionally examined by a physician to exclude those with symptoms clearly due to organic causes. The test-retest reliability of the tinnitus item in the Somatoform Disorders Schedule was 0.53 (kappa) and thus satisfactory.

Valid and complete protocols were available from a total of 1275 patients. 28% were males and 72% females with a mean age of 39.5 years (sd = 12.5). The assessment of diagnoses for somatoform disorders according to ICD-10 resulted in 24 cases of somatisation disorder (2%), 186 of undifferentiated somatoform disorder (15%), 314 of persistent somatoform pain disorder (25%), 269 of somatoform autonomic dysfunction (21%), 56 of hypochondriacal disorder (4%) and 245 of neurasthenia (19%). Somatisation disorder, somatoform autonomic dysfunction and neurasthenia are primarily

defined by multiple medically unexplained somatic symptoms. Undifferentiated somatoform disorder is a residual category for less severe clinical syndromes similar to those of somatisation disorder. Hypochondriacal disorder is defined by a persistent belief to suffer from a serious physical disease despite medical reassurance that there is no evidence for such a disease. Persistent somatoform pain disorder is diagnosed if severe and distressing pain is the main focus of the patient’s attention over a period of at least 6 months.

Study 2

This study investigated a total of 111 patients with chronic tinnitus who were treated either as inpatients in the Roseneck Centre of Behavioural Medicine or as outpatients in a nearby private ear, nose and throat practice, both facilities located in Southern Germany. The Roseneck Centre is described in more detail elsewhere in this volume (see Hiller, Goebel and Schindelmann: *Developing a structured interview to assess audiological, aetiological and psychological variables of tinnitus*). Although the private ear, nose and throat practice (E. Biesinger and colleagues, Traunstein) belongs to the regular German medical system and offers the usual neuro-otological services, it has become specialised during the past years for its diagnostic evaluation and treatment of acute and chronic tinnitus patients [11,12].

Our goal was to compare patients with compensated and decompensated tinnitus. While the term ‘compensated’ refers to persons who are able to cope with their tinnitus without showing clinically relevant psychological distress, decompensated patients are usually characterised by additional depressive, anxiety or psychosomatic symptoms [4]. 42 inpatients of the above sample had a score of 46 or more in the German version of the Tinnitus Questionnaire [13,14] and were classified as decompensated. 21 outpatients with less than 30 points in the TQ served as the compensated comparison group. Both groups did not differ significantly with respect to age, gender, familial and occupational status. The decompensated patients had a mean age of 50.2 years (sd = 11.0) and a female:male ratio of 45:55%, whereas the compensated tinnitus patients had a mean age of 47.0 years (sd = 13.1) and a female:male ratio of 38:62%. However, the lower grades of educational level was overrepresented in the decompensated group ($p < 0.01$). The tinnitus had been present for 6.5 years (sd = 6.4) in the decompensated and for 3.8 years (sd = 4.9) in the compensated group, but this difference was not significant at the 5% level. 64% of the decompensated and 48% of the compensated patients were found to have a clinically relevant hearing loss ($p > 0.05$).

Diagnoses of somatoform and other mental disorders according to DSM-IV were made by means of a structured interview and diagnostic checklists. These instruments have proved reliable in previous studies. Since dysfunctional beliefs towards and

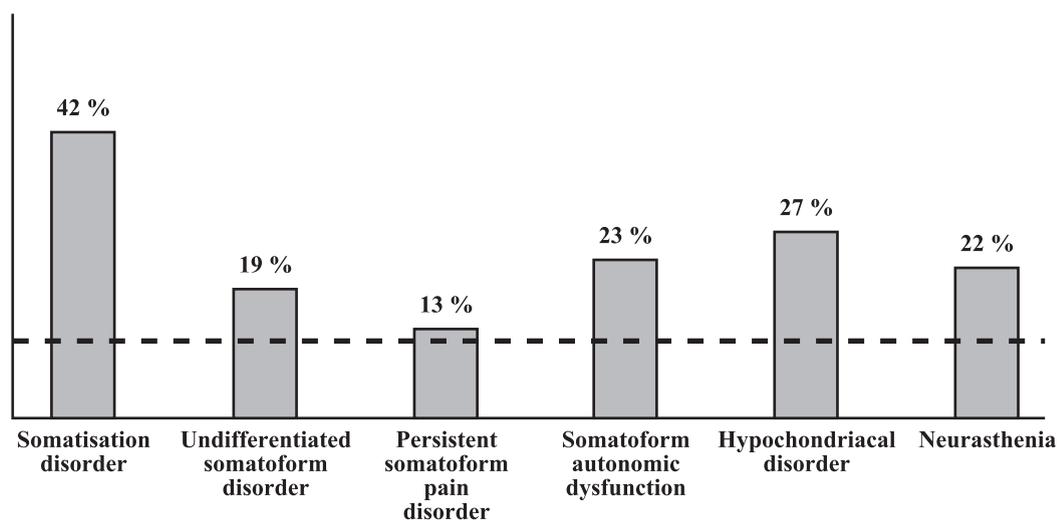


Figure 1 Frequency of tinnitus in patients with ICD-10 somatoform disorders. 11% had tinnitus in the unselected complete sample of the WHO study (dotted line)

interpretations of bodily symptoms were found to be typical for patients with somatoform disorders [15], we also administered a new, well validated and reliable questionnaire assessing such cognitions on dimensional psychometric scales (CABAH = Cognitions About Body and Health Questionnaire; German version see [16]). This questionnaire comprises the following scales: (1) catastrophizing interpretation of bodily complaints (e.g. 'the most common reason for discomfort is a serious disease'); (2) autonomic sensations (e.g. 'I often feel my heart beating because my circulatory system is very sensitive'); (3) bodily weakness (e.g. 'after physical exertion I often have a feeling of being weak'); (4) intolerance of bodily complaints (e.g. 'if something is wrong with my bodily sensations, it upsets me at once'); (5) health habits (e.g. 'I am always careful to live really healthily').

Results

Study 1

Across all centres of the WHO study, medically unexplained tinnitus was reported by 142 patients (11% of the total sample). Their demographic characteristics were: mean age 42.5 years (sd = 13.6), mean educational level 9.5 years of school (sd = 4.4), employment rate 55%. Significantly more females (77%) than males (23%) reported tinnitus ($p < 0.05$). Tinnitus patients were older than patients without tinnitus (42.5 *vs.* 38.9 years; $p < 0.05$) and less educated (9.5 *vs.* 11.1 years of school; $p < 0.01$), although there were no gender differences ($p > 0.05$). In addition to the group of 142 patients with medically unexplained tinnitus, clear organic tinnitus was found in 97 and sub-clinical (compensated) tinnitus in 162 cases.

In a next step, we analysed how often medically unexplained tinnitus was present among patients diagnosed as having one of the above mentioned

somatoform disorders. These results are summarised graphically in Figure 1. While the rate of tinnitus in the unselected complete sample was 11% (see dotted line), we obtained clearly higher percentages for somatisation disorder (42%), hypochondriacal disorder (27%), somatoform autonomic dysfunction (23%) and neurasthenia (22%). Thus, as tinnitus occurred more often in these groups, it showed a clear association with somatoform disorders. The rate of tinnitus in the group without any of the somatoform disorders in Figure 1 was only 5%. The tinnitus rates in the subsamples with vs. without somatoform disorder were significantly different (5% *vs.* 17%, respectively; $p < 0.01$).

Additional analyses showed that the symptom of medically unexplained tinnitus was most closely associated with the following somatoform symptoms (Phi correlations in brackets): trouble keeping balance (0.23), hot or cold sweats (0.23), blurred vision (0.23), dry mouth (0.22), bad taste in the mouth (0.21), burping or hiccups (0.20), shortness of breath (0.20), nausea (0.19), feelings of heaviness or lightness (0.17), lump in the throat (0.19), urinating too frequently (0.19), lost feeling in arm or leg (0.18), spells or attacks of shaking (0.16), joint pains (0.16). These correlations were significantly different from zero ($p < 0.01$). Of the 142 patients suffering from tinnitus, 45 (32%) suffered from a depressive disorder according to ICD-10 (assessed by means of the WHO Composite International Diagnostic Interview), whereas 97 (68%) did not. We also analysed the association between tinnitus and panic disorder which was found to be present in 15 (11%) of the tinnitus patients and absent in the remaining 127 (89%). These data show that in the majority of the cases tinnitus was not complicated by clinically relevant signs and symptoms of depression or panic anxiety, although the rate of about one third with an additional depressive disorder seems to be of clinical importance. Further details of our analyses have been presented elsewhere [17].

Study 2

In our study contrasting compensated and decompensated forms of tinnitus, we found that 48% of the patients with decompensated tinnitus also fulfilled the criteria of a somatoform disorder, whereas this was not the case for any of the patients of the decompensated subgroup. The complete comorbidity profiles of both groups are summarised in Table 1. Anxiety disorders as well as affective disorders, obsessive-compulsive disorder, eating disorder and alcohol use disorder were clearly more frequent in decompensated tinnitus patients. While 93% of the compensated group met criteria for at least one DSM-IV disorder, these were only 14% in the compensated group.

When single somatoform symptoms were analysed, we found that decompensated tinnitus patients reported more pain, gastrointestinal and neurological symptoms than the compensated comparison group (each comparison $p < 0.05$). The number of psychosexual symptoms did not differ significantly between both groups. Out of the 33 symptoms listed in the definition of DSM-IV somatisation disorder, decompensated tinnitus patients reported a mean of 5.0 lifetime symptoms ($sd = 3.9$), more than the compensated group with a mean of only 1.8 symptoms ($sd = 2.5$; $p < 0.01$). Decompensated tinnitus was most frequently associated with pain in the head (52%), back pain (45%) and abdominal pain (38%), whereas compensated tinnitus showed its closest relationships with back pain (38%) and frequent diarrhoea (24%).

Among the subsample of 20 patients with decompensated tinnitus plus somatoform disorder, the onset of the somatoform disorder was about eight years before the onset of the tinnitus. The mean onset age was 34.1 years ($sd = 12.6$) for the somatoform disorders and 42.2 years ($sd = 13.2$) for the tinnitus ($p < 0.01$). 14 of the 20 patients (70%) developed the somatoform disorder before the beginning of the tinnitus, whereas the remaining six patients had experienced their tinnitus before the beginning of the somatoform disorder.

Patients with tinnitus plus additional somatoform disorder were also more negative in their beliefs and attitudes concerning their general bodily functioning. The comparison of the scores in the CABAH questionnaire between both groups is given in Table 2. Decompensated patients showed a more catastrophizing interpretation of their bodily symptoms,

Table 1 Comorbidity of DSM-IV mental disorders in patients with decompensated and compensated tinnitus (percentage rates)

| DSM-IV disorders | Decompensated (n = 42) | Compensated (n = 21) |
|--------------------------------|---------------------------|-------------------------|
| <i>Any somatoform disorder</i> | 48 | 0 |
| Somatisation disorder | 17 | 0 |
| Undiff. somatoform disorder | 10 | 0 |
| Pain disorder | 14 | 0 |
| Hypochondriacal disorder | 17 | 0 |
| <i>Any anxiety disorder</i> | 64 | 14 |
| Panic disorder | 43 | 5 |
| Social phobia | 21 | 0 |
| Specific phobia | 5 | 14 |
| Generalized anxiety disorder | 29 | 5 |
| Posttraumatic stress disorder | 14 | 0 |
| <i>Any affective disorder</i> | 79 | 14 |
| Major depression | 57 | 14 |
| Dysthymic disorder | 21 | 0 |
| Obsessive-compulsive disorder | 5 | 0 |
| Eating disorder | 5 | 0 |
| Alcohol use disorder | 5 | 0 |
| <i>Any DSM-IV disorder</i> | 93 | 14 |

were more concerned with autonomic sensations and had a stronger self-concept of being bodily weak and disabled. Although there were no differences in the scales describing intolerance of bodily complaints and health habits, the overall total CABAH score was significantly higher in the decompensated tinnitus patients. These results confirm the hypothesis that dysfunctional cognitions in highly distressed tinnitus patients are similar to those typically found in somatoform patients.

Discussion and conclusion

Similarities between chronic tinnitus and the somatoform disorders have not been recognised by systematic research in the past. However, both conditions are characterised primarily by one or more physical symptoms which cannot sufficiently be explained by medical disease. Moreover, considerable psychological distress is a common feature that complicates the clinical picture. Since such factors have also been described in patients suffering from

Table 2 Dysfunctional beliefs and attitudes in decompensated and compensated tinnitus patients

| CABAH scales | Decompensated (n = 42) | Compensated (n = 21) | Significance |
|-----------------------------------|---------------------------|-------------------------|--------------|
| Catastrophizing bodily complaints | 21.0 (10.1) | 13.0 (9.1) | $p < 0.01$ |
| Autonomic sensations | 6.7 (3.2) | 3.4 (3.0) | $p < 0.01$ |
| Bodily weakness | 12.7 (4.7) | 6.8 (3.5) | $p < 0.01$ |
| Intolerance of bodily complaints | 8.9 (2.5) | 8.0 (1.5) | n.s. |
| Health habits | 8.1 (2.1) | 7.3 (2.3) | n.s. |
| <i>CABAH total score</i> | 57.5 (17.4) | 38.5 (15.6) | $p < 0.01$ |

chronic pain syndromes [18], a close relationship is seen between pain and the more general concept of the somatoform disorders [19,20].

The results of the WHO study presented here showed that tinnitus was more frequent in subgroups of patients fulfilling the criteria of a somatoform disorder. While the overall prevalence of tinnitus in the total sample of general medical outpatients was 11%, significantly higher proportions were found especially for patients diagnosed as somatisation disorder or hypochondriacal disorder. The second study with subgroups of decompensated inpatients and compensated outpatients confirmed that somatoform as well as other mental disorder were more frequent whenever tinnitus was experienced as very distressing. In most cases, the somatoform disorder had developed prior to the tinnitus. Decompensated tinnitus patients showed more dysfunctional cognitions associated with their bodily functioning, a finding that supports the assumption that similar psychological mechanisms may be effective in both chronic tinnitus and somatoform disorders [21].

In all, it can be concluded from the findings presented here that a clear overlap exists between tinnitus and somatoform disorders. However, since the exact psychophysiological processes and their interaction need further study, it remains open whether tinnitus itself should be considered as a somatoform symptom or whether the co-occurrence of both conditions is better considered a phenomenon of comorbidity. Autonomic overarousal or excessive attentional focus on the symptoms may be common mechanisms which could explain why many patients with somatoform disorders later also develop tinnitus.

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Outcome for tinnitus patients after consultation with an audiologist

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The dictionary definition of consult is “to give expert advice as a professional”. Patients seeking professional care for tinnitus naturally expect the initial consultation to be the first step toward successful management of their health problem. Unfortunately, they are often rather quickly dismissed with an inaccurate summary of their audiologic status (e.g., “there’s nothing wrong with you”), a poor prognosis for tinnitus treatment (e.g., “I can’t do anything to help you”) and/or inappropriate professional guidance (e.g., “You just need to learn to live with it”). We report outcome for an unselected series of over 200 patients presenting to a medical center audiology clinic for a formal tinnitus consultation by an audiologist with more than 20 years of clinical experience. More than 90% of the patients had previously sought, without success, medical treatment for their tinnitus. Prior to the tinnitus consultation, patients completed the Tinnitus Handicap Inventory (THI) and a comprehensive survey questioning the nature of their tinnitus and the affect it had on their daily activities. During a hour consultation, patients were given detailed current information on the causes of and treatments for tinnitus. Patients also had ample opportunity to ask questions about tinnitus and discuss their problem with the audiologist. The initial group was subsequently subdivided into patients who declined management following the consultation versus those who chose to pursue a formal treatment plan, such as Tinnitus Retraining Therapy. Then, 6 to 18 months after the initial consultation, outcome for all patients was measured using the THI and baseline survey. The majority of patients declined formal tinnitus management. This decision was inversely related to tinnitus severity. Outcome for this subgroup was significantly improved by the consultation.

Methods

Subjects were a series of over 200 patients presenting to an audiology clinic in a major medical center for the chief complaint of tinnitus. Each patient was initially scheduled for a one hour consultation with an audiologist experienced in the assessment and management of tinnitus. Prior to the consultation, patients completed a detailed questionnaire which requested information about the onset, type, and severity of tinnitus, the affect of the tinnitus on daily activities, and a general medical and otologic history. Each patient also completed the Tinnitus Handicap Inventory prior to their first contact with an audiologist.

Characteristics of the patient group are summarized in Table I. The majority of patients (almost three-fourths) declined enrollment in an extended treatment program. Comparison of patients who

did elect to enroll in an extended treatment program (e.g., Tinnitus Retraining Therapy) versus those who received the consultation, and sometimes follow-up diagnostic audiologic and tinnitus evaluation, showed equivalence in the times since the onset of tinnitus, the number of tinnitus types, and in age and gender distribution. Patients enrolling in extended treatment, however, were characterized by generally greater awareness of tinnitus, more hyperacusis, and were more likely to describe depression secondary to their tinnitus.

The consultation consisted of:

- in depth probing of the questionnaire items,
- a review of current thinking about the demographics of tinnitus, possible causes and factors influencing the perception of tinnitus, and treatment options,
- an explanation of previous audiologic findings (if available),
- ample opportunity for the patient to ask questions, and
- recommendations for further diagnostic assessment and/or treatment.

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Table 1 Selected characteristics of patients who received an initial consultation alone (72%) versus those who also enrolled in an extended treatment program (28%)

| Characteristics | Consultation (N = 170) | Extended Treatment (N = 66) |
|-------------------------------------|---------------------------|-----------------------------------|
| Age in years | 54.2 (sd 13.6) | 54.5 (sd 15.0) |
| Gender | | |
| males | 61.5% | 68% |
| females | 38.5% | 32% |
| Hyperacusis | | |
| no | 47% | 39% |
| yes | 53% | 61% |
| Time since tinnitus onset in years | 9.0 (sd 10.6) | 11.7 (sd 13) |
| Time aware of tinnitus | 75.3% (sd 30) | 87% (sd 20) |
| Depression | | |
| no | 53% | 31% |
| blue | 44% | 51% |
| yes | 3.6% | 18% |
| Number of types of tinnitus per ear | 1.62 (sd 0.9) | 1.83 (sd 0.77) |

During the consultation, patients were always given written information about tinnitus (plus a brochure from the ATA), and very specific advice to avoid silence and to utilize some form of environmental background sound. From 6 to 18 months after the consultation, patients who did not elect extended treatment were surveyed again regarding their tinnitus with the same instruments used initially. Our objective was to explore patient outcome with consultation as the primary audiological intervention.

Results

Figures 1, 2 and 3 illustrate a sampling of the data collected from patients before and after the consultation. The proportion of patients reporting the perception of tinnitus during less than 20% of a typical day increased significantly following consultation (Figure 1).

Rated severity of tinnitus on a scale from 0 (minimum) to 10 (maximum) was not profoundly altered following consultation, although more patients reported minimal, and less patients maximum, tinnitus severity.

The clearest differences before versus after consultation were noted for the THI. Data for two THI items (12F and 16E) are illustrated in Figure 3. In comparison to baseline data, fewer patients following consultation indicated that tinnitus made life difficult for them or made them upset. Fortunately, consultative intervention did not appear to adversely influence the patients' response to these items (no answers).

Conclusion

Our experience with an unselected population of patients presenting with tinnitus to an audiological clinic suggests that an extended consultation serves multiple clinical purposes. Perhaps first and foremost, the one hour scheduled visit immediately and effectively conveys to the patient the message that a professional is sincerely interested in their problem. Much consultation time is devoted to answering patient questions, and clarifying misconceptions, about tinnitus, and dispensing factual

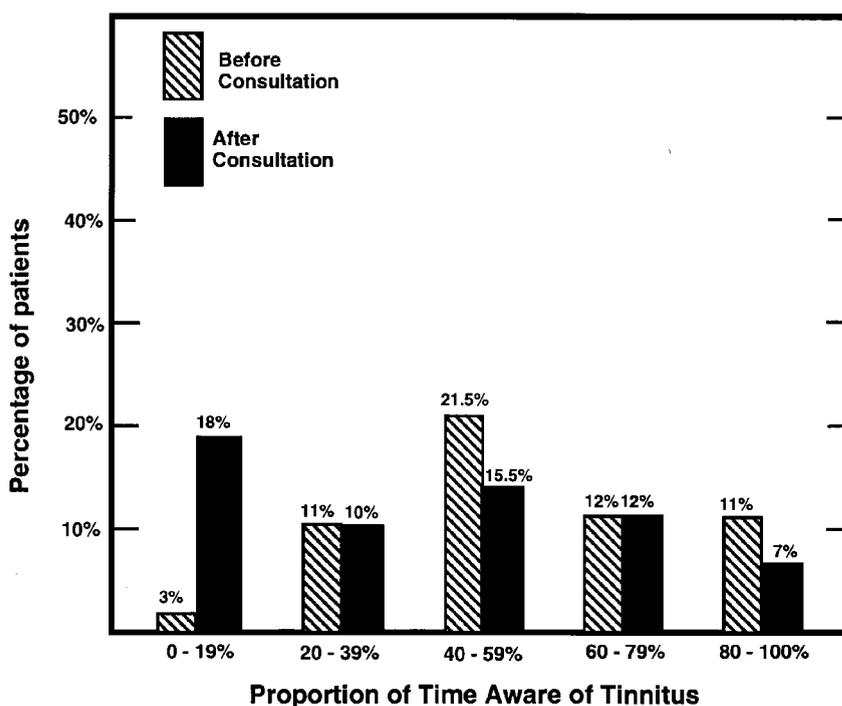


Figure 1

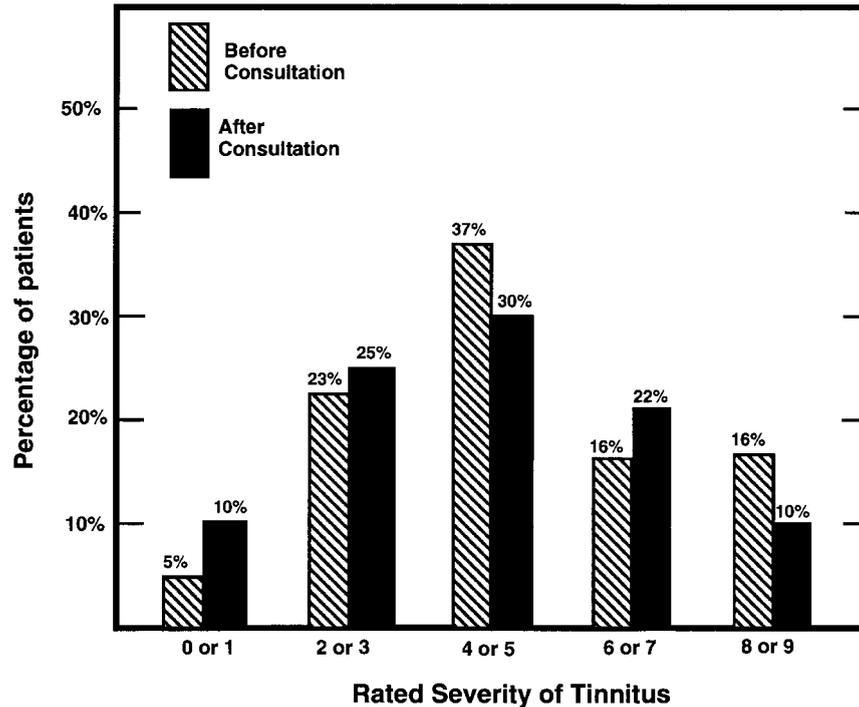


Figure 2

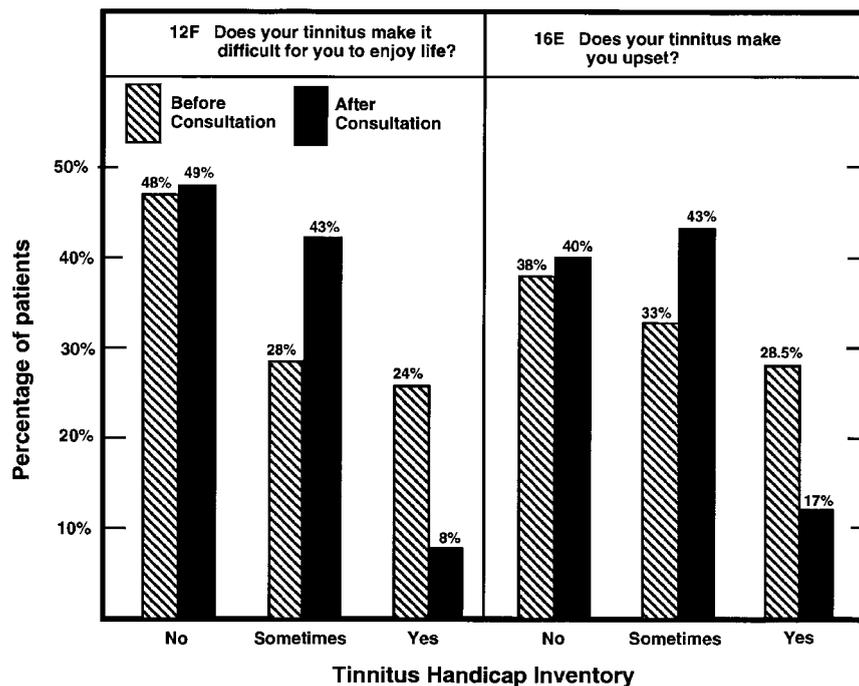


Figure 3

information about tinnitus and its treatment. The consultation also provides an essential opportunity to review in detail the patient's health history, and to make appropriate referrals for diagnostic medical and audiologic evaluations or treatments, and other indicated consultations. Finally, we provide

evidence suggesting that either the consultation itself, and/or the patient's compliance with simple recommendations made during this visit, can improve outcome and minimize the requirement for extended tinnitus treatment.

The role psychological and social variables play in predicting tinnitus impairments

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The purpose of this study was to investigate whether tinnitus impairments can be predicted by psychological and/or social variables. A sample of 153 patients with tinnitus (75 females, 78 males) were recruited from various treatment facilities in Austria and Germany. Patients were evaluated using the following instruments: Tinnitus Handicap Inventory (THI-12), Depression Scale (ADS-L), Quality of Life (WHOQOL-BREF), List of General and Somatic Complaints (BL), Health related Locus of Control Scale (KKG). The effects of depression, various dimensions of quality of life, somatic and general complaints, locus of control, as well as sleeping disorders were assessed on emotional-cognitive and functional-communicative tinnitus impairments using a canonical correlation analysis. It was shown that severity of depression is the most significant predictor of emotional-cognitive impairments due to tinnitus. Somatic and general complaints, physical and social domains of the quality of life scale, in addition to depression predict functional-communicative impairments. Of the variables studied depression seems to be a general dimension influencing tinnitus impairments.

Introduction

Due to the fact that tinnitus can not be sufficiently evaluated by medical examinations or by psychoacoustic measurements (i.e., loudness and pitch), it is important to consider psychological and social variables when assessing tinnitus patients. Only a small fraction of all patients with tinnitus are complaining about mood disorders, concentration problems, irritability, sleeping disturbances, etc., while most patients cope with their symptoms. The question is which factors identify patients who experience tinnitus as tolerable from those who suffer from tinnitus and complain about their condition.

In an other recent study, a sample of tinnitus patients admitted to a psychosomatic hospital, a high incidence of somatoform disorders were observed by Hiller *et al.* [1]. Further, a high prevalence of mood disorders were found among tinnitus patients in several studies [2,3]. The significance of effectively coping with perceived tinnitus symptoms was examined in previous studies. For example, Kirsch *et al.* [4] distinguished between subjects with a low or high capability of coping, and found

that patients with a low capability of coping were significantly more impaired than those with a high coping capability. Budd & Pugh [5] demonstrated that the perceived severity of tinnitus is positively correlated with an external locus of control, while a negative correlation was found between an internal locus of control and current tinnitus impairments. These studies underline the difficulty of identifying specific psychological and social factors influencing tinnitus impairments.

The purpose of this study was to examine how different patterns of psychological and social factors influence tinnitus impairments.

Methods

In this study fifty three patients suffering from chronic tinnitus participated (75 females, 78 males). The mean age was 51.6 years with a standard deviation of 14.5. Patients were recruited from the ENT-Department and the Tinnitus Outpatient Clinic of the General Hospital of Salzburg (Austria), and from an ENT-practice in Traunstein (Germany), as well as, from tinnitus self support groups during 1998. The patients had suffered from tinnitus for a mean duration of 71.4 months with a standard deviation of 98.1.

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Subjective tinnitus complaints were evaluated by the German version of the Tinnitus Handicap Inventory (THI-12) [6]. This instrument is comprised of 12 items (THI-total score) with two subscales, an emotional-cognitive (THI-emcog), and a functional-communicative (THI-fucom). Depression was measured using the ADS-L [7], a German version of the CES-D [8]. Quality of life was assessed with the WHOQOL-BREF [9] containing four domains; physical health, psychological, social relationships and environment. A standardized list of complaints (BL) [10] was used to identify somatic and general complaints. The locus of control, with respect to illness and health, was measured with the KKG [11]. This German instrument consists of three components: (1) internality (KKG-I, patient believes that he or she is responsible for health or illness), (2) social externality (KKG-P, patient prefers to contact persons of confidence or specialists), and (3) fatalistic externality (KKG-C, patient refers problems to fate/chance or God). Sleeping disturbances were detected with sleeping protocols (SP: in the evening before going to bed, and in the morning after waking up).

The data were analyzed using canonical correlation statistics. The canonical correlation tested whether psychological and/or social factors are significant predictors for tinnitus impairments and how they influence the two subscales of the Tinnitus Handicap Inventory (THI-12).

Results

The present study found that 59% of the variance of the emotional-cognitive subscale ($\text{canR} = 0.769$, $\text{Chi-sqr.} = 118.29$; $\text{df} = 22$; $p = 0.000$) can be explained by the depression factor (T for Beta = 2.8; $p = 0.006$). This indicates that patients scoring higher on the Depression Scale also show high levels of emotional-cognitive impairment. The variance of the functional-communicative subscale can be predicted by 20.7% ($\text{canR} = 0.4555$, Chi-

$\text{sqr.} = 24.42$; $\text{df} = 10$; $p = 0.006$) by the depression factor (T for Beta = 2.32; $p = 0.022$), the physical domain of quality of life (T for Beta = -2.67; $p = 0.009$), the social domain of quality of life (T for Beta = 3.11; $p = 0.002$) and by somatic and general complaints (T for Beta = 3.29; $p = 0.001$). This reveals that functional-communicative impairments are significantly correlated with, higher severity of depression, lower values in the physical domain of QOL, more somatic and general complaints, and higher scoring in the social domain of QOL. Significant levels were not reached by any of the locus of control variables or the sleeping disturbances.

Discussion and conclusion

Psychological factors such as depression, physical and social domains of quality of life, as well as, somatic and general complaints are appropriate predictors for tinnitus impairments. Depression was the best predictor for the emotional-cognitive tinnitus impairments. In contrast, somatic and general complaints, as well as physical and social domains of quality of life are shown to be good predictors for functional-communicative tinnitus impairments. Depression seems to be a general dimension influencing emotional-cognitive, as well as, functional-communicative factors of tinnitus impairment. The emotional-cognitive dimension is affected only by depression.

The results of this study are limited as depression is the only emotional state evaluated. Further studies are needed to explore the impact of various emotional states (e.g. anger, fear) on tinnitus impairments, and to examine the positive correlation between the social domain of quality of life and functional-communicative tinnitus impairments.

Acknowledgments: This study was financially supported by the Medical Research Society of Salzburg.

Table 1 T-statistics and Level of Significance for Betas Between Factors of Tinnitus Impairments and Psychological and Social Variables (Significant T-values are Printed in Bold).

| Psychological and Social Variables | T-statistics | | Level of Significance | |
|------------------------------------|---|---------------|--|-----------|
| | Tinnitus Handicap Inventory (THI-12) TBF-emkog | TBF-fukom | Tinnitus Handicap Inventory (THI-12) TBF-emko | TBF-fukom |
| ADS-L | 2.800 | 2.322 | 0.006 | 0.022 |
| QoL-phys. | -1.640 | -2.671 | 0.104 | 0.009 |
| QoL-psych. | -1.503 | -0.121 | 0.136 | 0.904 |
| QoL-soc. | 0.930 | 3.111 | 0.355 | 0.002 |
| QoL-environm. | 0.039 | 0.641 | 0.969 | 0.523 |
| BL | 0.780 | 3.292 | 0.437 | 0.001 |
| KKG-I | -1.713 | -1.653 | 0.090 | 0.101 |
| KKG-P | 0.534 | -1.382 | 0.595 | 0.170 |
| KKG-C | 1.043 | -0.947 | 0.299 | 0.346 |
| SP - morning | -1.572 | 1.260 | 0.119 | 0.210 |
| SP - evening | 1.719 | -0.540 | 0.089 | 0.590 |

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Changes in tinnitus distress over a four month no-treatment period: Effects of audiological variables and litigation status

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This study explored the effects of enrolling in a tinnitus clinic waiting list, and the influence of audiological factors and litigation status. Sixty-four participants completed longitudinal measures of tinnitus distress and state/trait anxiety before and after the four month no-treatment period. Amongst the non-litigation seeking participants, a small but significant mean improvement in tinnitus distress and state/trait anxiety had occurred. Litigation-seeking participants were found to have significantly greater distress, and a smaller percentage of improvement. None of the audiological factors appeared to distinguish the two litigation status groups, but an almost universal presence of very high frequency hearing loss was found.

Introduction

A dilemma experienced by tinnitus clinicians has been the uncertainty involved with counselling sufferers as to the likely time course of their tinnitus; i.e. whether they are likely in fact to “get used to it”, or conversely whether their fears of it becoming progressively worse might be founded. There is very little longitudinal data on changes in tinnitus distress which have been collected independently of potentially therapeutic sessions with a clinician.

Occasionally, some patients report spontaneous reductions in tinnitus disturbance, and so the identification of factors responsible for this needs to be determined. A patient’s audiometric configuration and anxiety levels can have a large bearing on treatment outcome, so these should be investigated as a potential factor in any form of spontaneous remission. There is the possibility that litigation-seeking tinnitus patients may be less likely to experience or report any reductions in tinnitus disturbance. However, an extensive literature review failed to locate any tinnitus studies that specifically identified compensation claimants in their data analysis.

It is possible that tinnitus distress might be able to resolve spontaneously, rather than as a result of

counselling or any other intervention. One large scale epidemiological study of tinnitus in the UK identified that a spontaneous reduction in tinnitus distress, or at least no deterioration, appeared to occur over several years in the majority of cases surveyed [1]. However, the time scale of this study might be too long to establish what proportion of any pre-post therapy improvements is due to spontaneous remission.

Contrary to the UK findings [1], a retrospective survey of 528 tinnitus patients found that severity and loudness tended to increase as a function of the number of years since onset [2]. However, they reported that their sample of hospital clinic referrals was unlikely to include those people whose tinnitus had substantially reduced or disappeared, and so reported that a longitudinal study was needed in order to determine the typical time course of untreated tinnitus.

Hallam *et al.* [3] predicted the attenuation of tinnitus distress over time as a result of reassurance, but a later study using a seven week waiting period did not support their earlier assertion [4]. Therefore, a further study that extends the measurement period to correspond with the new longer-term approach to therapy is needed. This has the potential to measure trends not so apparent in the short term, and so could provide more clinically applicable results.

An important counselling tenet is that while some spontaneous improvement can be expected over

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time, this process can be expedited by treatment [5]. Around one half of a sample of 163 patients reported a 2-year delay from their first perception of tinnitus until they experienced a moderate level of distress associated with it [6]. This suggested that negative beliefs might accumulate over time, which subsequently worsens the experience. Hazell [7] identified that negative counselling as to the prognosis of an individual's tinnitus can lead to an exacerbation of the distress associated with it. Thus, the acquisition of longitudinal data that supports the clinical observation that tinnitus distress is unlikely to get worse or "go on forever" would be very helpful for clinicians attempting to challenge these negative beliefs in their patients.

Several researchers have noted that patients with distressing tinnitus tend to have elevated anxiety levels [8,9], and so it is pertinent to note that the highly anxious patients are also the most responsive to clinical suggestion [10]. Thus, measurement of anxiety levels might help ascertain the underlying mechanisms of any group differences or changes in tinnitus distress.

Changes in tinnitus distress could be related to audiological factors, so this also requires further exploration. It is possible that localised hearing loss for the very high frequencies could be contributing to central gain of tinnitus from a lack of acoustic stimulation. One study has shown that virtually all tinnitus patients tend to display hearing loss in the very high frequencies [11]. Consequently, the present study will attempt to replicate this with more readily available equipment.

A consideration arising from a previous study by the present author [12] was whether litigation-seeking tinnitus patients are less likely to spontaneously improve, are less responsive to therapeutic intervention, or even less reliable in an experimental setting, in comparison with non-compensation claimants. One clinic reported that therapy is not performed on these individuals until their litigation is complete because they are less likely to improve [13]. An extensive literature review failed to locate any tinnitus treatment studies that specifically separated compensation claimants in their data analysis.

Hazell [14] indicated that anger and guilt are powerful emotions that might inhibit the process of tinnitus habituation. The legal process has also been reported to prolong a sense of grievance that could hinder a person's response to treatment [15]. Other clinicians propose that any belief that maintains the emotional significance of an individual's tinnitus is likely to prevent habituation from occurring [3]. The beliefs and attitudes of significant others about an individual's tinnitus has also been found to influence the habituation process [6]. Theoretically, compensation claimants might not habituate as readily if there are external legal circumstances that are maintaining a sense of anger or injustice as to how their tinnitus arose.

Conversely, there are many instances where compensation is clearly deserved, and the proceeds of this could also be used to offset the high cost of

treatment. It would therefore be useful for clinicians to be able to advise, on the basis of empirical data, whether the adversarial style of legal proceedings might actually serve to maintain the tinnitus longer than otherwise might be expected.

As a result of these issues, previous tinnitus research that did not exclude compensation claimants may have produced results that are not relevant for the majority of non-litigation seeking clinic populations. Therefore, the collection of data investigating this phenomenon has substantial implications for both research and clinical practice.

Methods

The original 90 Participants (Ps) were directly referred to the University Audiology Clinic by Ear, Nose and Throat Specialists ($n = 24$), Other Health Professionals ($n = 29$), or The Tinnitus Association of Western Australia ($n = 37$). They were required to have had an ENT consultation within the past five years to document the most likely cause of their tinnitus, and to rule out a medically treatable condition. Participants were excluded if they had begun any other treatment six months before the study, or subsequently began other tinnitus-related treatment during it, including new hearing aid fittings. They were also excluded if they had insufficient English language skills or cognitive ability to reliably complete the psychological questionnaires. Most of these criteria, and other factors such as litigation status, could only be determined at the first clinic assessment session after the baseline period.

Participants were initially informed about the nature of the research program by telephone. They were also told that the waiting list for the initial appointment was around four months. They were then posted a complete written outline of the research procedures, and a consent form. This included the statement that it was the faculty policy to not contribute to any matters of legal, compensation, pension applications or sickness benefit claims. Complete confidentiality of all findings was assured. If the Ps accepted the experimental conditions, they signed the consent section, completed the pre-baseline Tinnitus Reaction Questionnaire (TRQ) [16], and the Spielberger State/Trait Anxiety Inventory (SSAI/STAI) forms [17], and posted them back to the researcher.

Four months afterwards, their clinic appointment was arranged by telephone. They were posted a map to help locate the Tinnitus Clinic within the University grounds, and the second series of the TRQ, and the SSAI/STAI. These questionnaires were to be completed at home then brought along to their first clinic appointment.

At the post-waiting list clinical session, a complete audiological case history was taken, with special note made of their tinnitus' aetiology, time since onset, nature of onset (sudden/gradual), and hearing aid usage. Pure tone hearing threshold levels were tested with a Madsen OB822 Clinical Audiometer and Telephonics TDH 39 headphones.

These were calibrated to the relevant Australian standards, except for the 10 and 12 kHz signals, which were calibrated to the audiometer manufacturer's specifications [18] and re-confirmed on a normal population. The Oregon Tinnitus Clinic Protocol [19] was used to establish the psychophysical parameters of tinnitus pitch, loudness balance, minimum masking level, and residual inhibition. Test results were discussed in detail with each of the Ps, and they later participated in another project using counselling and music-based acoustic stimulation.

Results

Five Ps were excluded at the first assessment session; three Ps because they had insufficient English language skills or cognitive ability to reliably complete the psychological questionnaires, two Ps because of recent first-time hearing aid fittings, two other Ps withdrew, and another two Ps could not be contacted. At the end of the extended baseline, the number of remaining participants fell to a total of 81, and had a mean age of 49.1 years ($SD = 14.7$), ranging from 17 to 74 years. The gender ratio of participants was 48 males to 33 females.

There were four Ps whose response on the initial TRQ suggested suicidal ideation. It was decided that it would be potentially hazardous to request that they wait four months before therapist intervention began. These patients tended to be characterised by a sudden and unexpected onset of tinnitus in recent months, concurrent with clinically significant levels of depression and anxiety. Thus, they were seen immediately, given intensive counselling and choice of treatment types, and withdrawn from the waiting list data collection.

Thirteen Ps were identified as seeking, or having recently received, financial compensation directly as a result of their tinnitus. Positive litigation status was defined as those seeking a common-law claim

in relation to their tinnitus ($n = 5$), and those seeking or currently receiving a disability allowance ($n = 3$) or Veterans' Affairs benefit ($n = 5$) as a direct result of their tinnitus. These Ps were designated the Lit group, and the non-litigation Ps designated the Non-lit group.

In addition to the creation of an emergency non-baseline group, 10 other Ps did not complete their questionnaires at home, preferring to wait until their first session with the researcher to seek further clarification. Consequently, as the extended baseline was intended to be a measure of change irrespective of therapist attention, the Ps without both sets of questionnaires could not be included in the baseline data analysis. Therefore, a total of 64 Ps were available for the extended baseline data analysis, with 51 being non litigation-seeking Ps.

The TRQ scores were transformed using square root notation to satisfy paired t-test assumptions of normality and paired homogeneity of variance. Table 1 shows that the mean scores of the 51 Ps displayed clinically small (but statistically significant) reductions in tinnitus distress and state/trait anxiety over the four month no-treatment period.

As many clinical studies have expressed their results in terms of percentages, the data was then converted to this format, finding that tinnitus distress reduced by 15.2%, trait anxiety reduced by 5.3%, and state anxiety reduced by 6.2%. The TRT definition of significant habituation has been defined as a reduction of more than 30% in the amount of distress associated with tinnitus [20]. To explore the data in these terms, the extended baseline TRQ1-2 data was converted into the categories of Worse (>-6), Same ($<\pm 6$), Better ($>+6$), or Much Better (>30). These were compared with different severity groupings of Moderate (TRQ <50) and Severe (TRQ >50) distress. The distribution of this data is displayed in Table 2. Extrapolating from these results, a reduction in tinnitus distress over the baseline period occurred in 83% of those with severe distress, and 42.1% of those with moderate TRQ scores. Chi-square analysis found that the

Table 1 Tinnitus severity (TRQ) and trait state anxiety (STAI/SSAI) over the extended baseline period

| Measure | Initial mean | 16 week mean | <i>df</i> | paired <i>t</i> | <i>p</i> (2 tail) |
|---------|--------------|--------------|-----------|-----------------|-------------------|
| TRQ | 34.1 (18.3) | 28.9 (17.5) | 49 | 3.85 | 0.0003 |
| STAI | 45.2 (12.4) | 42.8 (12) | 49 | 2.35 | 0.0230 |
| SSAI | 42 (12.2) | 39.4 (11.7) | 50 | 2.61 | 0.0121 |

Note. Values in parentheses are standard deviations. Litigation Ps were excluded.

Table 2 Distribution of TRQ changes over the extended baseline

| Group | TRQ change distribution | | | |
|----------|-------------------------|----------------------|----------------------|---------------------------|
| | TRQ Worse (<-6) | TRQ Same (± 6) | TRQ Better ($>+6$) | TRQ Much better (<30) |
| Moderate | 13.5% (5) | 44.7% (17) | 39.5% (15) | 2.6% (1) |
| Severe | 8.3% (1) | 8.3% (1) | 83.3% (10) | 0% (0) |

Note. Values in parentheses are the corresponding number of participants. Litigation Ps were excluded.

group differences approached significance ($X^2(3, N = 50) = 7.4, p = 0.0613$). This suggests that those with the highest initial distress tended to display the greatest spontaneous improvement.

All the audiological measures were obtained from each P's ear with the most disturbing tinnitus. When the tinnitus was equal inter-aurally, the ear with the greatest hearing loss was chosen. The mean hearing threshold levels (Table 3) indicated that substantial hearing loss was generally only present for the very high frequencies (10 and 12 kHz). Only four of the 80 Ps were found to have normal hearing (<20 dB HL) for all frequencies.

Averaged hearing levels (PTA1) were first derived by calculating the mean thresholds at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 kHz, thus incorporating their complete peripheral hearing status. The three-frequency average of 0.5, 1 and 2 kHz pure tone thresholds (PTA2) was also calculated because of its relevance to speech reception and hearing aid suitability. Table 4 shows that there were no significant differences between the two groups on all audiological measures.

Table 4 also shows that the mean hearing levels were nearly within normal limits when only considering the frequency range of speech (PTA2).

However, the mean hearing loss was far greater when all frequencies were taken into account (PTA1), indicating the presence of very high frequency hearing loss in this sample of Ps with disturbing tinnitus. The mean time elapsed since onset of tinnitus was quite diverse for both groups, although there was a trend for the Lit groups to have had tinnitus for longer, perhaps because of the long-standing nature of the war veterans' tinnitus. There was no significant difference between the two groups' tinnitus pitch or the sensation level of their minimum masking levels.

Analysis of whether tinnitus onset was sudden or gradual found that the Non-lit group had a high incidence of sudden onset (60%), while the majority of the Lit group (61.5%) had a gradual onset. The differences between the groups was not significant ($X^2(1, n = 62) = 1.94, p = 0.1638$).

The TRQ group means and mixed-plot ANOVA results are displayed in Table 5, showing that there was a significant difference between Lit and Non-lit Ps on all baseline psychological measures apart from post-baseline Trait anxiety. The Non-lit group displayed a far greater reduction in tinnitus related distress over the baseline than the Lit group.

Despite the limitations of having only 13 Ps in the

Table 3 Mean pure tone hearing threshold – all Participants

| Mean dB HL | Frequency (Hz) | | | | | | | |
|------------|----------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| | 500 | 1000 | 2000 | 4000 | 6000 | 8000 | 10000 | 12000 |
| | 15.9 (18.3) | 16.2 (17.6) | 20.6 (21.2) | 33.7 (26.1) | 42.1 (26.9) | 41.3 (27.4) | 56.7 (28.3) | 60.1 (24.5) |

Note. Values in parentheses are standard deviations.

Table 4 Mean pre-therapy audiological measures of litigation and non-litigation seeking groups

| Measure | Group Means | | df | t | p |
|-----------------|-------------|--------------|------|------|--------|
| | Non-Lit | Lit | | | |
| PTA1 (dB HL) | 36.3 (19.6) | 46.1 (20.5) | 1,61 | 2.25 | 0.1229 |
| PTA2* (dB HL) | 22.1 (18.8) | 24.9 (24.0) | 1,61 | 0.25 | 0.6194 |
| Onset* (months) | 52.7 (61.5) | 80.6 (138.6) | 1,61 | 0.86 | 0.3567 |
| Pitch (kHz) | 7.8 (3.5) | 7.6 (2.7) | 1,50 | 0.02 | 0.8798 |
| MML (dB HL SL) | 20.5 (13.8) | 24.3 (10.0) | 1,60 | 0.89 | 0.3576 |

Note. PTA1 = 11 Frequency Mean (0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 kHz), PTA2 = Three Frequency Mean (0.5, 1 and 2 kHz). Values in parentheses are standard deviations. *denotes square root transformation of raw data was required to satisfy *t*-test assumptions.

Table 5 Comparison of litigation and non-litigation group means on psychological measures over the extended baseline

| Measure | Lit Status | | df | F | p |
|--------------------|----------------|--------------|------|-------|--------|
| | Non-Litigation | Litigation | | | |
| Pre-baseline TRQ* | 34.1 (18.3) | 56.5 (25.3) | 1,60 | 10.8 | 0.0017 |
| Post-baseline TRQ* | 28.9 (17.5) | 54.9 (23.3) | 1,60 | 16.15 | 0.0002 |
| Pre-baseline STAI | 45.17 (12.3) | 55.00 (13.9) | 1,59 | 6.15 | 0.0160 |
| Post-baseline STAI | 42.79 (12) | 49.15 (12.9) | 1,60 | 2.82 | 0.0982 |
| Post-baseline SSAI | 42.0 (12.2) | 56.7 (16.6) | 1,60 | 12.62 | 0.0007 |
| Post-baseline SSAI | 39.45 (11.7) | 49.9 (12.4) | 1,60 | 7.99 | 0.0064 |

Note. TRQ = Tinnitus Reaction Questionnaire, SSAI = State Anxiety Inventory, STAI = Trait Anxiety Inventory. Values in parentheses are standard deviations. * denotes square root transformation of raw data was required to satisfy ANOVA assumptions.

Non-Lit group, Mixed Plot ANOVAs were performed. For TRQ scores they found a significant group difference ($F(1,62) = 14.8, p = 0.0003$), with a significant decrease over time ($F(62, 1) = 14.47, p = 0.0003$). The interaction between the variables was not significant ($F(1,1) = 2.67, p = 0.1071$). State anxiety measures displayed a significant group difference ($F(1,60) = 11.86, p = 0.0011$), a significant difference over time ($F(60,1) = 8.79, p = 0.0043$), and the interaction was not significant ($F(1,1) = 2.11, p = 0.1511$). Trait anxiety measures had similar results, with significance found for group difference ($F(1,59) = 4.58, p = 0.0364$), over time ($F(59,1) = 9.92, p = 0.0026$), and not for interaction effects ($F(1,1) = 2.86, p = 0.0960$).

In terms of percentages, the litigation-seeking participants' mean state anxiety reduced by 12% and their trait anxiety by 10.6% over the four month period, thus showing greater improvements than the non-litigation group. Conversely, the Lit groups' mean tinnitus distress reduced by only 2.8%, which was considerably less than the 15.2% mean improvement in the Non-Lit group.

Discussion

In a sample representative of those seeking help from a specialist tinnitus clinic, distress was stable or reduced for 86% of Non-lit Ps over a four month extended baseline. Their mean tinnitus distress reduced by 15.2%, trait anxiety reduced by 5.3%, and state anxiety reduced by 6.2%. These findings could be quite useful in the counselling of tinnitus Ps who fear that their tinnitus will continue to get worse. It suggests that substantial comfort was derived from the perception that their tinnitus was going to be assessed and treated at a specialist facility. As this improvement occurred without any sessions at the clinic, it is likely to represent a non-specific treatment effect.

There was a trend that suggested that those with the highest initial distress tended to display the greatest spontaneous improvement. From a purely statistical perspective this phenomena might potentially be attributed to regression towards the mean, but in terms of counselling information, it indicates that enrolment in a tinnitus clinic waiting list was most beneficial for those with the greatest distress. With only 12% of all Ps displaying an increase in their TRQ scores, the data generally did not support the common fear of Ps that their tinnitus distress will continue to increase.

The mean improvements in trait anxiety levels over the wait list were somewhat surprising given that this was a construct which is usually considered to be a more stable personality feature [17]. It may, however, reflect the possibility that the onset of tinnitus had caused a profound increase in state anxiety levels, which led to an increase in trait anxiety as well. The act of enrolling in a treatment program may have been successful at reversing this process.

The marked audiometric and psychological diversity amongst the sample of participants'

appeared representative of the researcher's regular tinnitus clinic population. While there was a considerable range of general hearing levels, only four of the 80 Ps were found to have normal hearing (<20 dB HL) for all frequencies. A marked prevalence of hearing loss at 10 and 12 kHz was also apparent, consistent with the findings of Domenech *et al.* [11]. These results suggest that clinics that do not routinely measure these frequencies might underestimate the extent of damage to the auditory system. Several current theories of tinnitus pathogenesis have argued that hearing loss causes neurological compensation, which leads to an increase in tinnitus [21,22]. Consequently, if hearing loss is present for the very high frequencies only, acoustic stimuli for retraining might need additional high frequency energy to ensure that the widest possible range of neurones are stimulated. Support for this notion has recently been provided by other tinnitus researchers [23].

The dramatic differences between the litigation and non-litigation Ps' tinnitus distress indicated that the two groups needed to be analysed separately to preserve the relevance to the broader tinnitus clinic population. The experimental design attempted to eliminate the possibility of Ps deliberately misrepresenting their response to therapy by preventing the disclosure of results to any party. This was clearly stated in the Ps' information/consent form, and also verbally reiterated at the first clinical session. Consequently, the outcomes data indicated that their relative lack of improvement may have a less conscious basis. The data thus corroborated with the tenet of Wilson [24], who argued that the simple 'compensation neurosis' explanation cannot account for the full extent of distress associated with tinnitus in compensation claimants.

The proportion of those with distressing tinnitus that are seeking compensation may be surprisingly high, as 14.4% of the study's sample were in this category. If this proportion is also representative of the samples used in previous research, or in a typical tinnitus clinic caseload, the ramifications of this finding may be quite wide-reaching.

Conclusions

The extent of hearing loss in tinnitus patients is an important consideration for the planning of their rehabilitation [1,23]. The present study found evidence of generally unacknowledged levels of hearing loss in the very high frequency range. None of the other audiological factors appeared to significantly differentiate the two litigation status groups.

Another clinical implication of the research was disproving the commonly held fear that tinnitus will continue to get worse. Once patients had decided to obtain treatment from the specialist tinnitus clinic, a 15.2% reduction in tinnitus distress, a 5.3% reduction in trait anxiety, and a 6.2% reduction in state anxiety then occurred over the four month period. This occurred without any face-to-face contact with the audiologist or any other treatment, thus provid-

ing a useful longitudinal measure of how much spontaneous improvement in distress could be expected in tinnitus clinic patients. Its ramification for counselling is that clinicians in this setting can now state with greater certainty that the tinnitus is quite unlikely to get worse, even without subsequent treatment.

Overall, the significant differences (both statistical and clinical) between litigation and non-litigation claimants is an important finding in view of the fact that previously published tinnitus research has not controlled for this potentially large source of variability in response to treatment. Thus, other researchers may benefit from determining how many of their Ps were seeking litigation or monetary compensation, then re-analyse their data with litigation as an independent variable. Future research should also benefit from careful screening for litigation status, and the exclusion or separate analysis of these patients. Awareness of this confounding factor may also be helpful in the counselling of patients who are considering litigation because of their tinnitus. It also suggests that the legal process may potentially have a negative influence on response to therapy.

In conclusion, the study provided further positive counselling information for patients, derived from the longitudinal evidence that tinnitus distress generally decreases spontaneously over four months by around 15%, once patients are enrolled in a tinnitus clinic waiting list. It also provided longitudinal evidence that litigation-seeking patients' tinnitus distress may be less likely to improve than their non litigation-seeking counterparts.

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Does systematic noise stimulation improve tinnitus habituation?

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In addition to well established methods of counselling the noise generator seems to be a remarkable tool, which helps patients to reorient their attention to external acoustic stimuli. The study presented is planned to answer the question: Does systematic noise stimulation improve tinnitus habituation? The study compares the treatment outcomes of patients using a noise generator for half a year with the outcomes of patients who do not. Both groups received tinnitus counselling. The patients included are from a rehabilitation hospital and from ear, nose and throat practitioners. The design and method of the study is presented and preliminary results are reported.

Introduction

The study presented is planned to answer the question: Does systematic noise stimulation improve tinnitus habituation? The study is in process. We will report the design of the study, the current state of our work and preliminary data from participating patients and their outcome so far.

In combination with well established methods of counselling [1,2,3] the noise generator seems to be a remarkable tool to help patients reorient their attention to external acoustic stimuli [4,5,6].

The treatment principle of inhibiting tinnitus detection by systematic acoustic stimulation with a low level broad band noise – as proposed by Dr Jastreboff and Dr Hazell – promises a reduced duration to tinnitus perceptibility and to tinnitus annoyance. Can this decrease improve chances for stable and lasting symptom management?

One starting point of our study is that in Germany despite of the lack of controlled outcome studies there were high expectations concerning the use of a noise generator. In the past the fate of new approaches in tinnitus management could be described as: Waves of enthusiastic reactions in the public followed by deep scepticism towards the new method. That is why we try to contribute to a undistorted estimation of the situation.

The study presented compares the treatment outcomes of patients using a noise generator for half a year with the outcomes of patients who do not. Both groups received tinnitus counselling. The study was planned to involve patients of a rehabilita-

tion hospital and patients of doctors of ear , nose and throat medicine.

The study is supported by the Deutsche Tinnitus Liga and Siemens Audiological Technique which is providing prototypes of special noise generators, and by the Staatsbad Bad Meinberg. The final data analysis will be made by the Institut für empirische Gesundheitsökonomie, a research institute specialised in clinical studies. This institute also supported the design of this study.

Method

Our hypotheses are:

- that after 6 months people using the noise generator report a significantly less tinnitus annoyance than members of a control group;
- that people using the noise generator report significantly fewer hours per day of tinnitus perceptibility and a significantly lower level of tinnitus loudness than members of a control group.

The noise generator is a device that is worn behind the ear. It produces broad band noise. Additionally, patients with hearing loss receive a device that combines a modern digital hearing aid with a noise generator. Both features can be controlled independently. This device provides external stimulation of the ear and an additional tool for the self monitoring of tinnitus loudness.

We chose a pretest-posttest control group design. The study includes patients from two treatment settings, which represent different intensities of counselling and cognitive behavioural intervention:

- (a) patients from local ear, nose and throat practitioners who received a general 2 hour intro-

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duction in the model of tinnitus formation and tinnitus habituation and further counselling while they were using the noise generator

- (b) patients of an inpatient tinnitus management program who received intensive psychological and medical support including cognitive restructuring and – for those who were in need of it – conflict oriented group psychotherapy, hypnosis or pharmacotherapy.

We planned to randomly assign patients to experimental and control groups. A total number of 180 patients was to be included. The experimental group was to use a noise generator, if needed in combination with a digital hearing aid, for approximately 6 hours a day for six months. Binaural use of the noise generator took place in cases where binaural tinnitus or tinnitus perceived in the head was reported. If tinnitus was perceived in only one ear the noise generator was used in the monaural way.

The control group received a skin reflex biofeedback device as a placebo condition. The use of the biofeedback device as a placebo is based on the notion that biofeedback therapy does not reduce tinnitus annoyance any more than the usual psychological techniques such as progressive muscle relaxation or Autogenic Training.

Criteria for inclusion of patients in the study were:

- participants had to be suffering from chronic tinnitus with a total score in the Tinnitus Questionnaire [7] of at least 40, which excluded persons with lower levels of tinnitus annoyance and tinnitus related distress;
- Not admitted to the study were persons who applied for early pension, who were striving for financial benefits due to their impairment and thus might be refractory to improvement. This criterion is especially important in rehabilitation hospitals. In the rehabilitation hospital taking part in this study – the Brunnen-Klinik in Bad Meinberg – about 25% of the patients had to be excluded due to this criterion.

The following groups of variables were planned to be recorded at beginning of treatment, after a tinnitus management course, after a 6 months phase and in a 1 year follow up:

- audiometric data at the beginning, during and after treatment;
- Tinnitus-questionnaire [7];
- Beck Depression Inventory [8];
- Tinnitus Disability Index with kind permission by Prof Kroener-Herwig who developed this adaptation from the Pain Disability Index [3,9,10];
- patients self monitoring by noise generator, which as mentioned above, has a tool for self performed matching of tinnitus loudness;
- questionnaire on Tinnitus anamnesis (e.g. hours of tinnitus perceived, days off from work etc.);
- after the 6 months period a standard interview was held with question concerning tinnitus

loudness, tinnitus annoyance, convenience of the use of the devices, importance of tinnitus in everyday life, changes in relationships or work conditions induced by the patients and other topics.

After the 6 months treatment phase participants were informed how they could obtain further counselling plus a noise generator in order to complete their treatment.

Results

In February 1998 the first patients were introduced in the study. In the progress of the study we had to accept the fact that we could not motivate the outpatient participants to agree with the control group condition, because these participants had already been informed by their physicians and the media about a noise generator. More than 100 participants have already passed throughout the half year treatment phase. Viewing these data in July 1999, 16 participants had passed through the follow up.

As for the inpatient group we first asked them to consent to a randomised allocation to one of the two treatment conditions and to participation in the 3 additional therapy sessions after their stay in the hospital.

The drop out rate was about 10% in each group.

We are looking forward to presenting the complete results once the data collection is completed. Cautious interpretation of our available data suggests that:

- Most of the patients reported a significant reduction of symptoms during the half year treatment phase, which amounted to 1.7 units of standard deviation on the Tinnitus Questionnaire, about 0.7 units of standard deviations for the Beck Depression Inventory and about 0.5 units of standard deviations for the Tinnitus Disability Index. (Data here including participants from the rehabilitation hospital.) The experimental group showed slightly superior outcomes in the psychometric measures. A final analysis of data will indicate whether psychometric measures show significant differences between control group and experimental group supporting our hypothesis.
- After the 6 months treatment phase we asked: "How many hours a day do you perceive tinnitus": about 25% of the members of control group, but more than 35% of the members of experimental group reported that they perceived tinnitus less than 8 hours a day.
- Self induced changes in everyday life, for example reducing work stress or solving conflicts in relationships, had an impact on the self reported annoyance by tinnitus after the six months treatment phase. Nearly 50% of the participants reported substantial changes in everyday life. 95% of the patients with such changes remarked a reduction of tinnitus annoyance, while only 75% participants with-

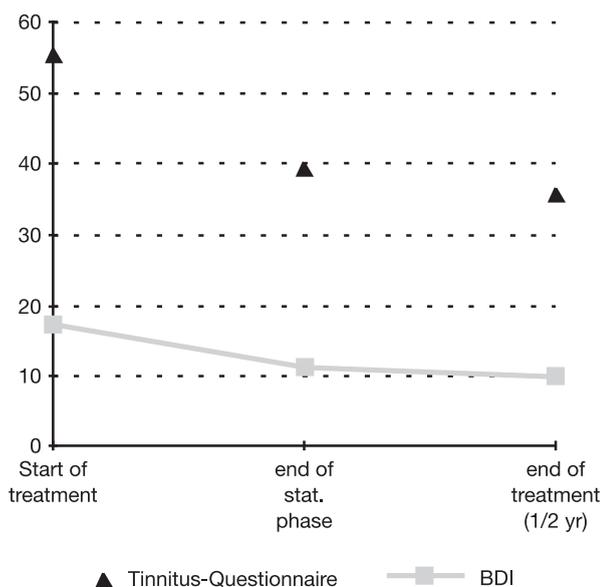


Figure 1 Psychometric measures

out such changes indicated a reduction. In our opinion psychosocial stressors play a dominant role in tinnitus annoyance, can inhibit tinnitus habituation and are a moderator variable in our study.

- 31% of the experimental group and 4% of the control group reported that tinnitus had lost its importance in their lives.

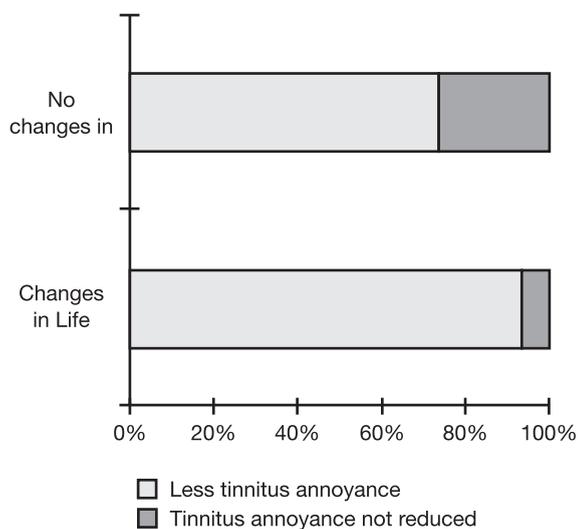


Figure 2 Self induced changes in everyday life and tinnitus annoyance

Discussion and conclusion

One point can be definitely stated: Patients reported that they experienced the noise generator as a con-

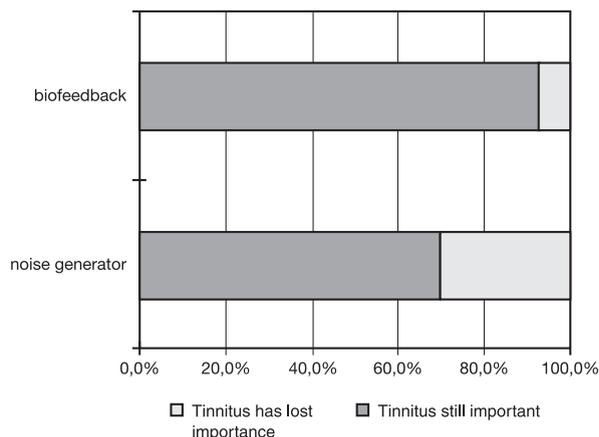


Figure 3 Importance of tinnitus after treatment

venient aid in learning to live with tinnitus and to manage tinnitus. Very often participants described the noise generator as an easy to use and efficient help in focusing attention on other stimuli than tinnitus.

In fact, systematic noise stimulation is a valuable tool in accomplishing tinnitus habituation.

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Categories of the patients in TRT and the treatment outcome

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The neurophysiological model of tinnitus indicates five main categories of patients and accordingly five variants of the treatment, using Tinnitus Retraining Therapy (TRT). The criteria for classification and these categories will be presented. Moreover, it should be expected that the effectiveness of treatment will vary depending upon the patient's category. Of particular interest was the theoretical prediction that the presence of hyperacusis can be a positive or negative factor, depending upon the presence of prolonged worsening of the symptoms as a result of sound exposure ("winding up" effect). Accordingly, patients seen at the University of Maryland Tinnitus & Hyperacusis Center have been classified into appropriate categories and evaluated before and after the treatment using questionnaires. The evaluation has been focused on the impact of tinnitus and/or hyperacusis on a patients' life and on the extent of tinnitus habituation. Consequently, specific attention has been paid to the patient activities that were affected or prevented by tinnitus and separately hyperacusis, percentage of tinnitus awareness, and on the effect of tinnitus on a patient's life, its severity, and annoyance (assessed on scale form 0 to 10). Included in this presentation are patients who accepted the TRT protocol and followed it, including follow-up visits.

In all categories patients exhibited improvement in those measures as documented by group averages and shifting of the cumulative distributions of the parameters studied. Notably, patients with hyperacusis who did not exhibit prolonged sound-induced worsening showed fast recovery and a higher proportion of those patients reached our criterium of significant improvement.

On the basis of the neurophysiological model of tinnitus and hyperacusis, it is possible to indicate several factors, which might be important for categorization of a patient and choosing proper variants of the treatment. Five major categories of patients are distinguished, but they should be treated as general guidelines only. The first factor considered in placing patient in one of the five categories, reflects the strength and stability of the connections between the auditory, and limbic and autonomic nervous systems. If the connections are weak, it should be possible to reverse or change them relatively easily. Careful consideration should be paid during patients counseling not to provide information which could enhance the importance of tinnitus, and as a consequence enhance connections between the auditory and the limbic and autonomic nervous systems. Patients who belong to this category do not experience a high level of distress from the tinnitus. This reflects the situation where changes in the plastic modification of the synaptic connections are stable, but at the same time, those

connections are not particularly strong. The other situation with weak connections happens in case of patients heavily stressed, but since their tinnitus developed not long ago (a span of weeks), it was not enough time for establishing permanent connections between the various systems involved in the processing of the tinnitus-related neuronal activity.

The second factor is the subjective perception of hearing loss. If the hearing loss is subjectively important to the patient, then problems with hearing in everyday life results in the "strain-to-hear" phenomenon, and an increased level of stress and discomfort. This in turn might enhance the perception of tinnitus and its impact on a patient's life. Additionally, in a patient with unilateral deafness, it is important to reactivate the parts which are not active due to the lack of auditory input and to re-map receptive fields of neurons in the auditory pathways [1].

The third factor is the presence of hyperacusis and/or phonophobia. Both phenomena, which are not recognized and discussed at the sufficient level, are discussed separately [2] and each requires different approach for its treatment. Note, that when hyperacusis is present, it typically prevents the use of sound levels which otherwise would be recommended for the treatment of tinnitus. If hyperacusis

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is not treated, and an attempt is made to treat tinnitus with sound therapy it will yield enhancement of hyperacusis and development of phonophobia.

The final parameters reflect the presence and duration of worsening of tinnitus and/or hyperacusis as a result of exposure to a sound. Sometimes a single exposure to a loud sound aggravate tinnitus and/or hyperacusis for a prolonged period of time (“kindling”). A similar phenomenon described as a “winding up” effect occurs when prolonged period of sound exposure results in the exacerbation of tinnitus and/or hyperacusis, while a shorter exposure to the same sound is without any effect. Categories of patients and main points of the treatments are presented schematically in Table 1.

Category 0 consists of patients who do not have hyperacusis, do not have significant hearing loss, and whose tinnitus has a little impact on their life. For these patients, the directive counseling session, including the advice to avoid silence and to enrich their sound environment, is usually sufficient. There is no need for any instrumentation. Patients with a recent onset of tinnitus, not exceeding more than two months, and who have not received any “negative counseling” [3] belong to this category as well.

Category 1 consists of patients who have significant tinnitus, but no hyperacusis and no subjective hearing loss. For these patients the most effective approach is the use of sound generators set at the level close to the “mixing” or “blending” point, e.g. when the external sound provided by generators and tinnitus can be heard separately, but start to interfere or intertwine with each other [4].

Category 2 consists of patients with the characteristics of Category 1 with the addition of significant subjective hearing loss. For these patients to achieve improvement in both tinnitus and hearing, hearing aids, typically programmable, are recommended. The patients are instructed to wear hearing aids all the time, while assuring enrichment of their sound environment. It is stressed to patients that sound is important for the treatment and not the hearing aids. The main purpose of the hearing aids is to amplify sound, while providing better communication is secondary.

Category 3 consists of patients with significant hyperacusis, which is not being enhanced for a prolonged period of time as a result of sound exposure. Tinnitus may, or may not, be present. In this case sound generators are highly recommended to help desensitize the hyperacusis. The desensitization procedure begins with the sound level set close to, but clearly above, the threshold of hearing, with the attempt to avoid problems resulting from stochastic resonance [1,5,6]. The sound is increased during the treatment to the level appropriate to their tinnitus (if present), or to the comfortable tolerated level. These patients tend to recover faster than patients with tinnitus only and the results show that successful treatments offers the cure for hyperacusis.

Category 4 consists of patients who have tinnitus and/or hyperacusis and exhibit prolonged worsening of their symptoms as a result of sound exposure. This is the most difficult category to treat. In this case, we set the level of sound generators at the threshold of hearing in spite of stochastic resonance. In cases where there is general hypersensitivity of perception of any type, not just to sound, the patients are advised to wear the devices for a week without turning them on. This is done in order to desensitize the patient’s perception of the touch to devices in their ears. As the treatment progresses, the sound level is increased very slowly. These patients need continuous monitoring and typically exhibit profound phonophobia.

Since both counseling and sound therapy are different for each category of patients, the question is asked if it is possible to observe systematic differences between the treatment outcome for various categories. Obviously, it is possible to expect a patient from Category 4, who additionally has a medical problem that can be linked to tinnitus (i.e., Lyme Disease), would be difficult to treat, but on the other hand successful medical treatment should facilitate tinnitus habituation.

The presence of hyperacusis in Category 3 and 4 might offer an advantage as it is possible to expect that by decreasing abnormal gain within the auditory neuronal pathways a decrease in the patient’s

Table 1 Categories of patients

| Category | Impact on life | Subjective hearing loss | Hyperacusis | Prolonged sound induced exacerbation | Treatment |
|----------|----------------|-------------------------|-------------|--------------------------------------|--|
| 0 | low | — | — | — | counseling |
| 1 | high | — | — | — | sound generators set at mixing point |
| 2 | high | present | — | — | hearing aid with stress on enrichment of the auditory background |
| 3 | high | not relevant | present | — | sound generators set above threshold of hearing |
| 4 | high | not relevant | present | present | sound generators set at the threshold; very slow increase of sound level |

Abbreviations: ‘Hyperacusis’ – significant sensitivity to environmental sounds typically associated with LDLs below 100 dB HL; ‘Prolonged sound-induced exacerbation’ of tinnitus/hyperacusis when the effects persists to the following day; ‘Subjective hearing loss’ – perceived subjectively by a patients as having a significant impact on patient’s life; ‘Impact on life’ – the extent of impact of tinnitus on patient’s life; ‘Treatment’ for each category always involves counseling and the use of enriched auditory background.

stress level should be achieved, as the patients would be able to function in a normal environment in a much better way. Additionally, lowering of the gain might result in a decrease in the strength of the tinnitus signals.

Evaluation of treatment outcome is very complex due to the lack of objective methods in detecting tinnitus and assessing its severity. A variety of methods have been proposed and are used in various centers, with common use of questionnaires [2,7]. Typically, a criterion is utilized to divide a group of patients into two subcategories: those who demonstrate "a significant improvement", defined in a variety of ways, and the others. On the basis of this division "a success rate" is reported.

Another approach is to combine the data from all patients, and present some parameters describing these data before, during, and after treatment. The first approach is predominant in reports describing the treatment of tinnitus, even though the second approach seems to be more objective, and allows the reader to judge the treatment outcome.

It is crucial to recognize that any improvement expressed in numbers, characteristics, or other physiological or psychological measures is meaningless, if a patient did not subjectively perceive the improvement in their everyday life. Therefore we are promoting an approach where evaluation assesses the impact of tinnitus and/or hyperacusis on a patient's life, with the additional stress put on the analyses of activities prevented or interfered with by tinnitus and/or hyperacusis.

Results from a total of 223 patients seen at the University of Maryland Tinnitus and Hyperacusis Center by a team consisting of WC Gray, DE Mattox, PJ Jastreboff, S Gold, K Humayun, were evaluated. For the purpose of this presentation, only patients who received some form of instrumentation (e.g., sound generators or hearing aids), and who were interviewed with the use of a previous version of standard forms (developed circa 1996), have been selected. All reported patients were interviewed using the same standard forms as a guideline, during the initiation visit and follow-up visits. To be included in this study, a patient had to be evaluated within a time window from ½ to 3 years. The following parameters were analyzed: (1) number of activities prevented by tinnitus; (2) percentage of time the patient was aware of tinnitus; (3–5) Assessment on a scale of 0 to 10 of the severity, annoyance and effect of tinnitus on their life. For this presentation, results which were obtained during the latest, but still within the time window visits were used. As the number of cases with hearing aids and Category 4 patients were small, these results were analyzed and described when appropriate, but not discussed in detail.

Inspection of the cumulative distributions for each of the parameters obtained before initiation of the treatment for the total population in each of the subcategories revealed some interesting features. There was no significant differences between distributions of these parameters describing different patients' categories, suggesting that the effects of

tinnitus do not depend on our categorization. The median values for severity, annoyance, and impact on life were in the range of 5 to 7 (on 0 to 10 scale). These distributions were uniform, after crossing the value of about 3–4, with approximately 10% of patients reporting values of these parameters equal or less than this point. This finding indicates homogeneity and continuity of the response population, with an indication that the value of about 3 might correspond to the threshold for clinically-relevant tinnitus.

The functional dependence is more complex for awareness. In addition to threshold value, which might be associated with awareness 20–30% of the total time, a rapid increase of the number of cases was observed for values greater than 90%. A potential explanation is that patients who are severely affected by tinnitus tend to believe that they are perceiving tinnitus all, or nearly all the time. Moreover, distinction should be made between being aware of tinnitus (which was our question), versus being aware and annoyed by it. Recently we included in our questionnaire an additional question aimed at awareness accompanied by annoyance [7] and indeed results obtained so far show clearly a smaller percentage of time when patients are annoyed by their tinnitus. This value might be a more realistic assessment of awareness.

All the data on delineating populations of the patients are consistent with a postulate that there is a smooth continuum of the extents with which tinnitus affects patients, and any attempt to classify patients as having significant *vs.* non-significant tinnitus, is highly disputable. While some threshold values may be indicated for educational purposes, they are rather non-precise, fuzzy, and should not be used for decision regarding treatment.

To assess the effect of the treatment, the individual differences for each subject were calculated by subtracting the initial value for each parameter from the value recorded during the following-up visit are presented as a percentage of the initial value. Analysis of the cumulative distributions of those changes pointed out some interesting facts. The most interesting finding is that the distribution of changes is flat, reflected in slightly nonlinear, concave cumulative distribution, with some additional nonlinearity noted for 20–40% of relative change. This indicates that there is a smooth continuum of the extent of improvement, without any clear demonstration of a threshold value, which could be associated with improvement.

Median change was about 50%, with the exception of severity, which showed smaller changes. It is not a surprise, as severity is closely linked to tinnitus loudness, which is not affected by TRT. A subjective assessment by the patient that tinnitus is less of the problem, may decrease their perception of tinnitus loudness and its severity.

Notably, while there is no significant difference between groups, there is a consistent tendency for patients with hyperacusis to have a larger extent of improvement. This finding supports both the theoretical prediction and clinical impression that

Category 3 patients tend to have a higher probability of improvement, and that recovery occurs faster.

The reoccurring question is what should be used as a criterium for “significant improvement”. We proposed in the past use of criterium of at least two of listed above parameters by at least 20%, in addition to having at least one life activity returning to normal, previously prevented or interfered with by tinnitus [8]. The criterium was based on intuitive assessment and correlation of our measures with subjective reports of the patients of experiencing improvement, they considered significant.

To assess the validity of this criterium or to find out a better one, the percentage of the patients who experienced improvement in any of recorded variable by a given extent (from 0 to decrease by 100%) was calculated (Figure 1). Only about 1% of patients reported no improvement or worsening for all parameters. At the same time 14% reported decrease of at least one parameters to zero (100% change). The very smooth curve again confirms that we are analyzing a gradual continuum of responses, without any clear, well-defined threshold of the border. Half of the patients reported the change of at least one parameters by 65%. There is clear and close to level of significance tendency for larger improvement in patients with hyperacusis (Figure 1, dashed line), as compared with tinnitus only (Figure 1, dotted line). Additionally twice as many hyperacusis patients experienced decrease of

one of the evaluated parameters to zero as compared with Category 1 (22% vs. 11%).

While there is no clear indication of any threshold value which could be accepted as a threshold a careful inspection of the cumulative distribution indicates an interesting possibility. The slope of curve is changing around point corresponding 40% change and 80% of population. This indicates the possibility that we are observing two overlapping population. Notably, this point closely corresponds to 82% of patients who reported self-perceived improvement (dashed line). Accidentally, our previously proposed criterium gives very similar value for “significant improvement” (81%).

Until an objective method of assessment of the extent of tinnitus is available, the optimal approach, allowing for the comparison of data from different groups, would be utilizing questionnaires containing the same questions, and presenting data in the form of distributions rather than means, percentages of success rate according to any criterium. Presented data argue strongly that at the moment we cannot accept any specific value as justified by anything better than coincidence with patients self report; indicating however, that with analyzing of larger number of cases it might be possible to distinguish two populations of changes, with an indicated threshold of transition between these two populations corresponding to patients subjective report of self-improvement.

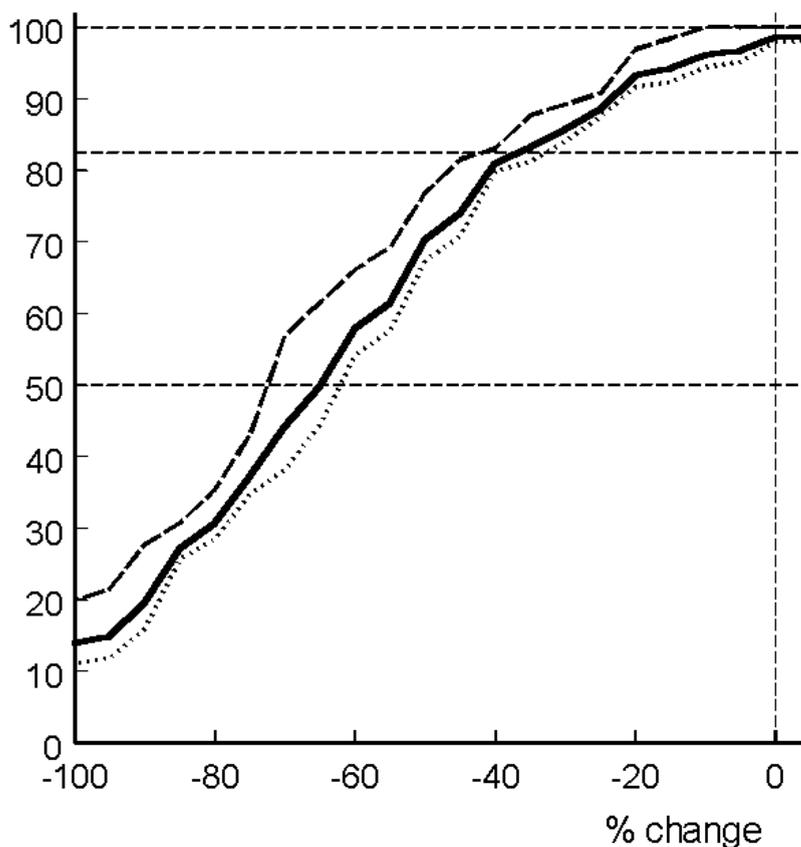


Figure 1 Cumulative distribution of patients experiencing given level of improvement for at least one parameter. Solid line presents the average for all population. Horizontal dashed lines show median, and the proportion of self-reported improvement. Note smooth functional dependence, and that patients with hyperacusis (dashed line) exhibit tendency to larger improvement, than patients with tinnitus only (dotted line).

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Combining elements of tinnitus retraining therapy (TRT) and cognitive-behavioral therapy: Does it work?

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In this ongoing controlled treatment study elements of cognitive-behavioral therapy (CBT) and tinnitus retraining therapy (TRT) were combined to provide different group treatments for different target populations of patients depending on the degree of tinnitus distress. In addition, half of the subjects in each treatment received sound therapy by behind-the-ear (bte) broadband noise generators to examine a possible therapeutic effect of additional auditory stimulation. Preliminary results show the effectiveness of both treatments, but no effect of sound therapy. One possible reason for the latter could be that only a small number of not severely affected patients have so far received treatment plus sound therapy. Another explanation could be the short period of time the devices have been worn so far.

Introduction

In the chronic tinnitus therapy as it is practiced today, at least in Germany, there are two main traditions of habituation therapies. On one hand, a number of psychological, cognitive-behavioral programs have been established and proven to be effective [1–3]. These programs focus on coping with and habituating to tinnitus and are designed for more or less severely affected patients. On the other hand, the so-called “Tinnitus Retraining Therapy” (TRT), which is said to be a quite effective new method of habituation therapy [4,5], has become widespread in the last few years. TRT consists of two main components, directive counseling (or “teaching”) and sound therapy, which simply means enrichment of the auditory environment [6]. The latter can most easily be realized by using behind-the-ear (bte) broadband noise generators. There is some discussion about the benefits and limitations of both approaches [7] and attempts have been made to define the differences between them [8]. But in fact both share a focus on habituation as a central goal of treatment and combinations of them may be quite frequent in daily practice [9].

When we first developed our concept for the

psychological treatment of chronic tinnitus at the psychological outpatient department of the University of Mainz, the two most important ideas became clear very soon. The first one was to adjust psychological programs to different populations depending on the degree of tinnitus distress. In other words, each of our patients was to receive the right “dose” of treatment. The second idea was to combine existing psychotherapy programs with elements from the neurophysiological approach of TRT.

We therefore developed the following concept with three levels of treatment:

First, there are some patients with a very low degree of tinnitus-related distress, who nevertheless seek consultation. These subjects only need a single appointment to ask questions and to make sure they know enough about tinnitus. They already have adequate coping strategies. No further treatment is necessary. This population is not subject of our studies.

Second, there are patients who have some problems in dealing with tinnitus, but are not severely handicapped. For this population, we devised an educational training called “Tinnitus Information” (TI). TI is a group treatment with four 90-minute sessions on hearing basics, tinnitus and its treatment. The neurophysiological model of tinnitus and its implications for every-day life are explained in detail. In accordance with this model, all patients are instructed to enrich their auditory environment

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and to avoid silence. Additionally, the “vicious cycle” and “coping cycle”, common elements of most cognitive-behavioral programs, are elaborated and applied to each participant’s personal situation. All patients are invited to ask all open questions, to discuss the course materials and to compare their experiences with those of the other participants.

The third level of treatment addresses severely handicapped patients experiencing significant psychological distress due to tinnitus. For this population, we designed the “Tinnitus Habituation and Coping Training” (THC). THC is also a group treatment, but with 10 sessions of 120 minutes each. In addition to the elements of the TI treatment, it includes a number of more or less “classic” elements of cognitive-behavioral therapy (for example, relaxation training, changing of dysfunctional cognitions, attention-focussing etc.).

Our ongoing study examines the additional effect of acoustical stimulation by noise generators. We present some first results here.

As previously stated, sound therapy or enrichment of the auditory environment is one of two main components of TRT. This additional stimulation of the auditory system can most easily be realized by noise generators, wearable like hearing-aids. But the use of a special device is not considered absolutely necessary and the effect can also be reached by carefully avoiding silence and using environmental sounds for reinforced stimulation, such as street-noise, music, radio etc. [6]. Nevertheless, there are some advantages of wearable sound generators. First, they provide a stable, comfortable signal which can easily be ignored since it contains no real information. Second, they can be worn everywhere and on all occasions. The resulting question is: do patients wearing devices show greater reductions in tinnitus-related distress than those who were only instructed to avoid silence and to enrich their auditory environment? This question is also of special interest regarding the growing number of devices sold, which are partly paid for by health insurance (in Germany).

Methods

Design

The design of our ongoing study which addresses the above questions is presented in Table 1. Half of the subjects in both conditions receive behind-the-ear broadband noise generators, one for each

Table 1 Design of our study with the desired number of cases and (in brackets) the number of patients treated and examined so far.

| | “Tinnitus Habituation and Coping Training” (THC) | “Tinnitus Information” (TI) |
|------------------|--|-----------------------------|
| Sound Therapy | N = 30 (N = 0) | N = 30 (N = 16) |
| No Sound Therapy | N = 30 (N = 8) | N = 30 (N = 11) |

ear, without any costs arising for the patients. All patients are randomly assigned to the groups after careful diagnostic examination.

Our design was chosen to investigate the following two hypotheses:

- (1) Both group treatments lead to significant reductions in all measures of the patients’ tinnitus-related distress.
- (2) There is an additional therapeutic effect for those subjects in both treatments who are not only instructed to enrich their auditory environment but who are also wearing noise generators.

All the subjects in the sound therapy-condition are instructed on how to use the devices and to wear them as often as possible, especially in silent environments. All further instructions follow the common guidelines for the use of noise generators in TRT [6]. We use behind-the-ear broadband noise generators (especially designed for our study by the hearing-aid manufacturer Interton GmbH, Bergisch Gladbach, Germany) with individual earmolds (produced by Audioplast GmbH, Offenbach, Germany) to make sure that wearing the devices is as comfortable as possible and does not interfere with hearing. This cannot be achieved with in-the-ear devices. The noise generators provide a volume control for the patients’ use, starting from zero, as well as frequency- and volume-presets to adjust the sound to different audiological features.

Assessment

For a basic assessment of our patients we use the “Structured Tinnitus Interview” (STI) [10] and the German version of the Tinnitus-Questionnaire (TQ) [11]. We further assess some audiological parameters (hearing threshold, loudness discomfort level and minimal masking level).

The TQ is used to identify the severely affected patients. It is also our main instrument in measuring therapeutic effects. It measures global tinnitus distress as well as several scales, such as emotional distress, cognitive distress, intrusiveness etc. Other instruments which we use before and after the treatments include the “Tinnitus Diary” and the “Tdys” questionnaire. The diary consists of four questions which are to be answered on a visual analogue scale (0–100) every evening. The most important question is “How loud was your tinnitus today?”. The Tdys questionnaire was especially designed for this study to assess dysfunctional beliefs and attitudes concerning the tinnitus. 33 cognitions such as “Someday this sound will drive me mad” or “If my tinnitus gets worse, it will damage my hearing” are listed. The patients can express the degree of agreement on a scale from 0 (“I don’t agree”) to 4 (“I totally agree”).

Sample

Until now we have treated a sample consisting of 35 adult outpatients (16 women and 19 men) suffering

from chronic tinnitus. The mean age was 51.5 years (sd = 13.6) with a range from 23 to 73 years. All patients suffered from tinnitus that can be characterized as chronic, i.e. lasted six months or more, and was due to different etiologies such as sudden hearing loss, acoustic trauma, otosclerosis, Menière's disease etc. All patients had been referred to our treatment by their ENT physician or because of a local newspaper article describing our work. It was ascertained that ENT examination was completed and no standard medical treatments for the tinnitus were indicated.

Eight subjects showed specific audiological dysfunctions. Five of them had a mild hearing loss, four on both ears, one only on one ear. None of these hearing losses was significant regarding interference with speech discrimination. Two patients had one deaf ear, with no hearing loss on the other ear in one case, the other patient wore a hearing aid on the other ear. One patient wore hearing aids in both ears. To make these three cases as comparable as possible to the others, we had the fitting of the hearing aids controlled.

Hyperacusis was diagnosed in 10 patients as reported by themselves and measured by loudness discomfort levels.

Results

As it can be seen from Table 1, we intend to assess and treat a total of 120 subjects in the long run. We will also follow our patients for two years after the end of treatment. Since our programs began in January 1999, we can only report some preliminary data for 35 subjects before and after three different treatments for now: THC (N = 8), TI without sound therapy (TI; N = 11) and TI with sound therapy (TIplus; N = 16). Because of the small number of cases we decided to refrain from any broader statistical analysis and present our results in descriptive terms.

The changes in tinnitus distress in the different treatment groups as measured by the various instruments are shown in Table 2 and 3. The results for all three treatment modalities show a reduction in tinnitus-related distress. A good example and maybe the most important score is the global score of the TQ: it dropped from a mean of 51.2 to 33.8 in the THC group, from 27.3 to 12.7 in the TI

Table 2 Changes in tinnitus distress as measured by the TQ (global score), the Tdys (global score) and the tinnitus diary (perceived loudness) in 8 patients before and after the "Tinnitus Habituation and Coping Training".

| | Before mean (SD) | After mean (SD) |
|----------------|---------------------|--------------------|
| TQ | 51.2 (5.1) | 33.8 (8.1) |
| Tdys | 36.8 (8.9) | 22.8 (7.9) |
| Tinnitus-Diary | 61.1 (16.5) | 54.1 (19.9) |

group and from 34.9 to 17.2 in the TIplus group. Despite the fact that the TIplus group started from a higher lever of distress as measured by the TQ, no differences in the extent of reduction of tinnitus distress can be seen between this group and the group without sound therapy (see Figure 1). Similar findings were obtained for all other measures.

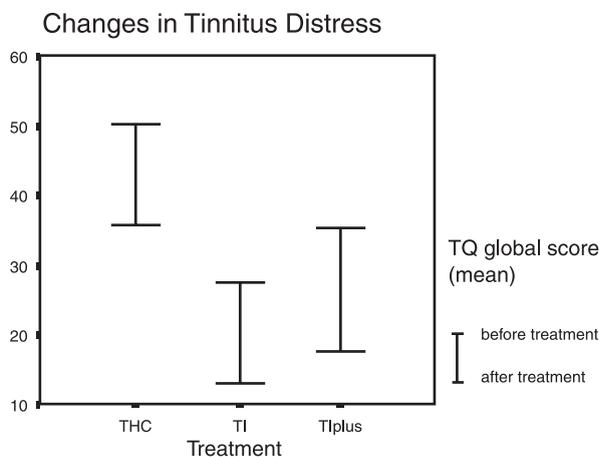


Figure 1 Changes in tinnitus distress as measured by the global score of the TQ. The scores for three groups of patients in three different treatments are shown: Tinnitus Habituation and Coping Training (THC), Tinnitus Information (TI) and Tinnitus Information with additional auditory stimulation by noise generators (TIplus).

The acceptance of the noise generators in the TIplus condition is very satisfying. No complaints about incorrect fitting have been made so far, after a short introduction all subjects were able to put the devices into place and handle them. Some remaining questions about how to use them exactly have been cleared in the group sessions. One subject

Table 3 Changes in tinnitus distress as measured by the TQ (global score), the Tdys (global score) and the tinnitus diary (perceived loudness) in 27 patients before and after the "Tinnitus-Information".

| | Sound Therapy | | | |
|----------------|---------------|-------------|--------------|-------------|
| | No (N = 11) | | Yes (N = 16) | |
| | Before | After | Before | After |
| | mean (SD) | mean (SD) | mean (SD) | mean (SD) |
| TQ | 27.3 (6.7) | 12.7 (7.4) | 34.9 (11.1) | 17.2 (8.3) |
| Tdys | 27.9 (11.7) | 18.4 (8.9) | 32.3 (11.0) | 16.0 (7.9) |
| Tinnitus-Diary | 46.0 (13.5) | 34.9 (19.5) | 47.4 (20.0) | 35.9 (18.8) |

returned the devices, not due to any complaints about the generators themselves, but to himself always forgetting to wear them and finding it very annoying to think of it. The subjects in the TIplus group wore the devices an average of 6.9 hours per day (sd = 4.8) as reported in the tinnitus diary after treatment.

Discussion and conclusion

As mentioned before, we are intending to treat a total of 120 subjects for our final analysis. Follow-up assessments will be conducted for two years. With reference to the hypotheses outlined above, two preliminary conclusions can be drawn at this point of time:

- (1) There is evidence for both of our programs being effective in reducing tinnitus distress. The reduction in the various measures and especially in the global score of the TQ is as large as reported by other studies before [3]. It is particularly surprising that such a change could be achieved in only four weeks in the TI treatment. An important question is, whether these effects can be confirmed and whether they will be stable over a longer period of time. We feel confident to reach this goal after the promising first results presented here.
- (2) No additional therapeutic effect due to the auditory stimulation by noise generators can be shown so far. However, for two reasons it is too early to draw conclusions on the effect of noise generators at this time. One is that we only have data on a small number of subjects in the TI treatment with noise generators, but sound therapy may be of greater benefit to more severely handicapped patients. The other reason is that we examined these patients only four weeks after receiving the noise generators. This could simply be too short of a period of time for a change in the auditory system.

One global conclusion we would like to draw is that we can see no basic contradictions between TRT and the already established cognitive behavioral treatments for chronic tinnitus. In contrary, it seems very useful to combine elements of these two approaches in order to treat specific subgroups of patients. Our personal experience is that TRT's strong emphasis on teaching the patients a comprehensible (neurophysiological) model of tinnitus and on the importance of increased stimulation of the auditory system (however this may be realized) are valuable additional components to established educational and psychological programs.

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Real-ear measurement of the sound levels used by patients during TRT

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In approximately 70% of Tinnitus Retraining Therapy (TRT) patients, special sound generators are recommended. These are broad band noise generators (BBNGs) which are either worn behind the ear with an open mold fitting, or instruments which are inserted in the ear canal in an unoccluded configuration.

Introduction

The use of real-ear measurements in a Tinnitus Retraining Instrument (TRI) fitting has two purposes:

- (A) To determine the change in resonance in the ear canal and whether or not the change alters the individual's hearing with the device in place;
- (B) To assess the amount of sound generated by the device in situ.

The following was assessed using real ear measurements:

- (1) The effect of occlusion on the ear measurement of Tinnitus Retraining Instrument (TRI) in the ear canal;
- (2) Changes in the frequency response of the broad band noise instruments (BBNI) in situ over time;
- (3) Monitor the level of BBNIs during TRT program.

REMs were performed on approximately 20 patients and typical findings are presented.

In reference to (1) the REMs allow assessment of the amount of occlusion occurring with the insertion of the TRI or an ear mold, used with the BTE devices. Subsequently, either one can be modified if ear canal resonance is altered significantly. Figure 1 shows three recordings: a Real Ear Unaided Response (REUR), an initial recording showing significant change in the resonance upon insertion of the instrument, and a third recording obtained with a corrected TRI. The amount of occlusion in

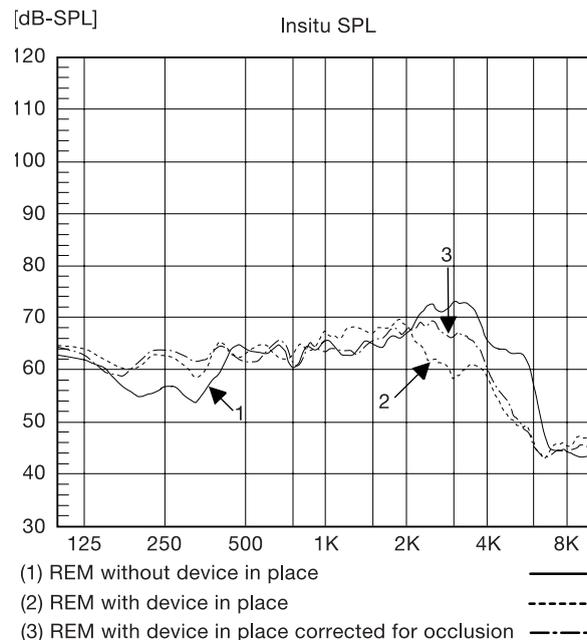


Figure 1 Occlusion effect

the corrected TRI is significantly reduced. Therefore, use of REMs allows us to assess the extent of interference of a BBNI in the ear canal, and for verification of any corrections to reduce occlusion.

These measurements can also be used to demonstrate to the patient that, in fact, his or her resonance of the ear canal remains essentially unchanged with the use of the TRIs. This has been found to be a useful counseling technique.

With respect to (2) the REMs allow us to monitor the frequency response of the tinnitus instrument in order to determine:

- (a) The stability of the frequency response over time;
- (b) Presence of spikes in the frequency response;

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- (c) Stability of the frequency response with jaw and head movement; and
- (d) Changes in the sound level over time during the TRT program.

Figure 2 shows a recording of broad band noise taken over 60 seconds in three 15-second intervals. It is evident that the output from the noise generator is not stable. Figure 3 depicts a faulty instrument with intensity spikes. We also observed a dramatic change in the frequency response with excessive jaw movement. This was easily corrected by shortening the canal portion of the device. In another patient, we observed a change in the frequency response due to head movement. This was again corrected by remaking the ear mold to insure a good retention of the ear mold in the concha.

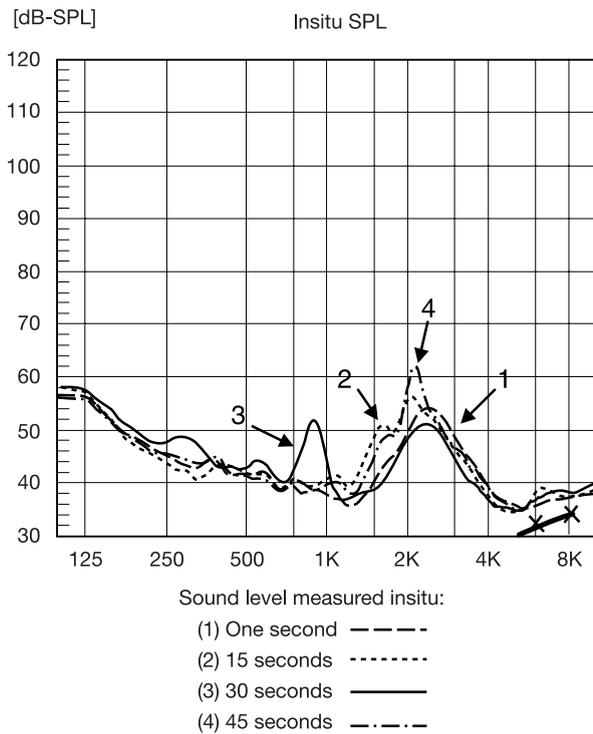


Figure 2 Temporal characteristic of tinnitus instrument

To establish validity of real ear measurements and the stability of the BBNGs, the recordings were performed at each follow-up visit. Notably, it was found that in patients who exhibited habituation there was a decrease in the output of the BBNGs over time. This observation could be attributed to changes occurring with processing of tinnitus-related neuronal activities due to habituation. Simultaneously, these patients also reported subjective decrease in the Severity/Annoyance Rating of their tinnitus.

The neurophysiological model of tinnitus proposes that habituation of tinnitus, which is the goal of Tinnitus Retraining Therapy (TRT), results from the modification of processing of tinnitus-related neuronal activity. One of the levels involved in the processing of this activity is the subconscious part of the auditory pathways. At the same centers of the auditory pathways the suppression of tinnitus by external sounds occurs. The minimal level of

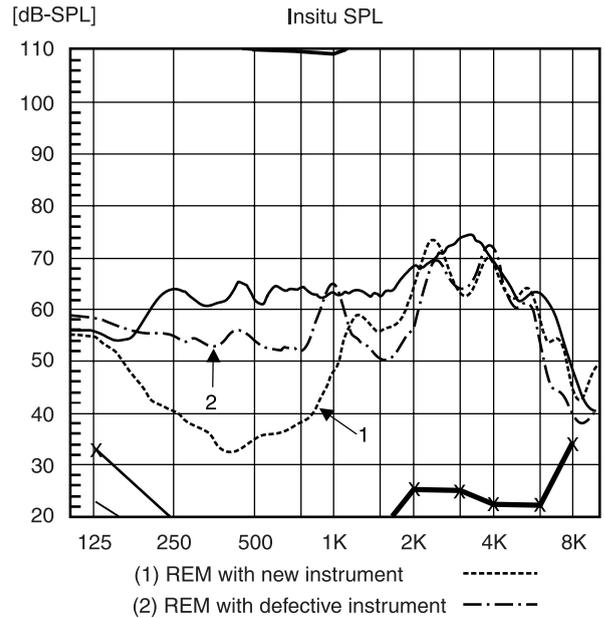


Figure 3 Faulty instrument

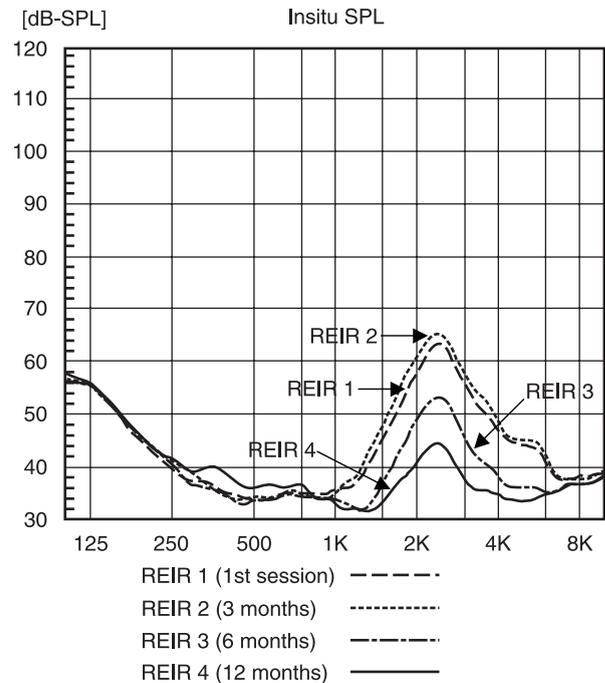


Figure 4 Patient No. 1: 48-year-old male

external sound needed to suppress tinnitus perception reflects minimal signal-to-noise ratio when detection of tinnitus is still possible. Neuronal networks processing signals within the auditory pathways are initially well tuned to discriminate the tinnitus-related neuronal activity from the background neuronal activity. During the treatment these networks are gradually de-tuning, and a lower level of external sound is sufficient to suppress tinnitus [1].

Indeed, this prediction has been confirmed by clinical data, which showed that minimal suppression level ("Minimum Masking Level") has decreased significantly in patients who showed

Table 1

| Patient No. 1: 48-year-old male | | | | | |
|---------------------------------|--------|--------|--------|---------|---------|
| | Outset | 3 mos. | 6 mos. | 12 mos. | 18 mos |
| % of Time* | 100% | 100% | 50% | 20% | n/a |
| Severity | 7-8 | 7-8 | 5 | 3 | n/a |
| Annoyance | 7-8 | 8 | 4 | 2 | n/a |
| Effect on Life | 4 | 4 | 3 | 1 | n/a |
| Patient No. 2: 72-year-old male | | | | | |
| | Outset | 3 mos. | 6 mos. | 12 mos. | 18 mos |
| % of Time* | 90% | 90% | 70% | 50% | 20% |
| Severity | 7-8 | 7-8 | 7 | 5 | 3 |
| Annoyance | 7-8 | 7 | 6 | 4 | 3 |
| Effect on Life | 7 | 6 | 4 | 3 | 2 |
| Patient No. 3: 68-year-old male | | | | | |
| | Outset | 3 mos. | 6 mos. | 7 mos. | 10 mos. |
| % of Time* | 70-80% | 50% | 20% | 60% | 20-30% |
| Severity | 7 | 4 | 2 | 6 | 3 |
| Annoyance | 7 | 4 | 2 | 6 | 3 |
| Effect on Life | 5 | 3 | 1 | 4 | 2 |
| Patient No. 4: 69-year-old male | | | | | |
| | Outset | 3 mos. | 6 mos. | 12 mos. | 18 mos. |
| % of Time* | 80% | 50-60% | 40-50% | 20-30% | n/a |
| Severity | 6-7 | 4-5 | 4 | 3 | n/a |
| Annoyance | 7-8 | 5 | 4 | 3 | n/a |
| Effect on Life | 3 | 3 | 2 | 1 | n/a |

* = % of time device being worn

All patients included here have successfully completed TRT.

improvement, and increased in those who did not improve [2]. While significant, these changes were rather small and could not be used to monitor the treatment progress in individual patients.

Another measure, however, could be more sensitive to changes in the processing of tinnitus-related activity. As a part of sound therapy, patients are advised to wear noise generators, with the sound level set at, or slightly below, the “mixing/blending” point. Psychoacoustically, this is the minimal sound level at which partial suppression of tinnitus signal by neuronal network begins. The sound and its level used by patients can be evaluated using real-ear measurement.

The first four patients on whom REMs were performed and who finished TRT are presented. Subjective patient responses on Dr. Jastreboff’s standard questionnaire are presented in Table 1. All patients showed significant improvement of their tinnitus. All of them exhibited the decrease of the sound level used at a given stage of the treatment. While it might be coincidental, it might reflect detuning of the filtering properties of neuronal networks involved in tinnitus detection. (Figures 5-7.)

All recordings were performed in an Industrial Acoustics sound isolation booth. Special attention was paid to the real ear probe placement, insuring the same length of insertion for each measurement.

Preliminary data from those who are still in the treatment process indicate that changes in the

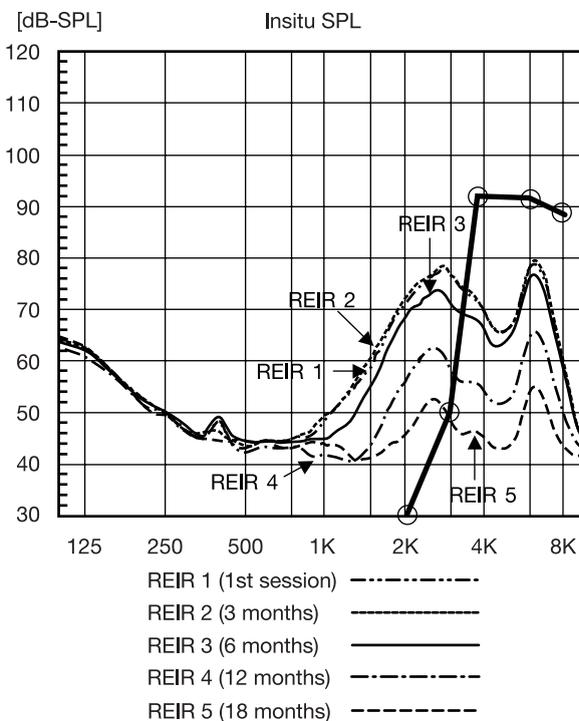


Figure 5 Patient No. 2: 72-year-old male

sound level of the noise generators appeared to be correlated to the treatment outcome.

Several mechanisms might be responsible for observed changes, and work is in progress to deter-

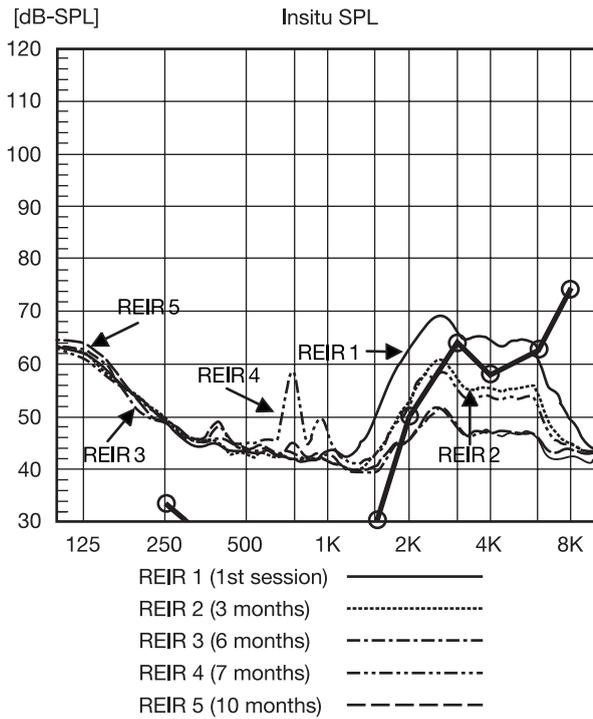


Figure 6 Patient No. 3: 68-year-old female

mine whether, indeed, modification of the processing properties within the auditory pathway is a dominant factor. Nevertheless, these results indicate a potential usefulness of real-ear measurements of actual sound levels used by patients for monitoring progress of the treatment.

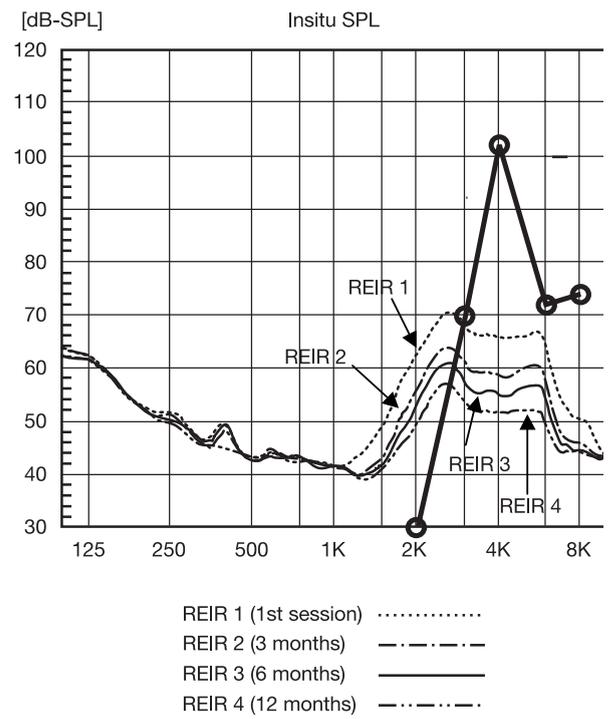


Figure 7 Patient No. 4: 69-year-old female

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The effects of hearing loss on tinnitus

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Tinnitus perception and reaction were measured in 182 individuals who received five sessions of TRT in a 12 month period, and 159 followed up after a further 12 months. This study group was divided into three on the basis of hearing status — normal hearing (NORM), mild high—frequency hearing loss (HF), and moderate to severe hearing loss (MOD/SEV). The MOD/SEV group reported that their tinnitus had worsened prior to the study, whereas the NORM and HF had started to habituate to their tinnitus. At the start of the study the MOD/SEV group had significantly greater loudness and percentage awareness, tinnitus pitch was significantly lower, and number of tinnitus sounds significantly higher than the NORM and HF groups. After 12 months of TRT, tinnitus annoyance, effect on life quality, loudness and percentage awareness in each hearing status group improved by a similar amount. Psychological status was measured in a representative sub—group of 118 individuals. Phobic anxiety in both males and females, and depression in males were positively correlated with hearing threshold at 4000 Hz. It is possible that hearing threshold influences tinnitus reaction, perception and psychological status but it does not appear to influence response to TRT significantly.

Introduction

People with hearing loss are almost three and a half times more likely to have tinnitus than those with normal hearing [1]. There is evidence that hearing loss influences the degree of annoyance tinnitus causes [2], and that hearing loss may be one of the factors that determines whether or not individuals seek treatment for tinnitus [3].

Hearing loss may influence tinnitus in several ways. Firstly, damage to the auditory system may increase the strength of tinnitus generators. Secondly auditory deprivation resulting from hearing loss may serve to increase central auditory sensitivity to these generators. Thirdly hearing loss may cause a significant psychological impact [4]. Increased arousal and emotional distress associated with this psychological effect, and “straining to hear” may serve to enhance tinnitus detection.

The cochlea is susceptible to physiological damage, and is involved in all forms of sensori-neural hearing loss. There are numerous theories relating tinnitus generators to peripheral auditory damage. These include damage to outer and inner hair cells, stereocilia decoupling, cross talk between inner and

outer hair cells, ionic imbalance involving calcium, and changes in efferent activity [5,6,7].

Moller [8] has noted that damage to the peripheral auditory system leads to a decrease in spontaneous activity in the auditory nerve. This results in hyper—responsiveness to sound in the inferior colliculus and other brainstem nuclei [9,10,11]. Jastreboff [7] suggested that this increased sensitivity occurs in response to any input, including normal spontaneous activity which may result in tinnitus perception.

Increased sensitivity as a result of reduced peripheral input may explain why individuals with a hearing loss are more likely to experience tinnitus. Often the pitch of tinnitus occurs around the frequency of the greatest degree of hearing loss [12]. Reduced input from one particular area of the cochlea may result in increased sensitivity of neurons tuned to the corresponding frequency region. Increased sensitivity to internally generated sound has also been noted in individuals with normal hearing placed in a soundproofed booth [13]. This indicates that increased sensitivity is caused by reduced peripheral input rather than peripheral damage.

Altered mood state (particularly anxiety and depression) is often associated with tinnitus distress [14,15,16]. McKenna [4] reported that 45% of individuals complaining of tinnitus had a psychological disorder (in comparison to 64% of those complaining of vertigo and 27% of those complaining of hearing loss). High levels of anxiety and depression were also found in tinnitus clinic

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patients by Stephens and Hallam using the Crown-Crisp Experiential Index [16].

Psychological disturbance, such as anxiety and depression, may serve to increase arousal and emotional distress. Hallam *et al.* [17] suggest that during periods of high central and autonomic nervous system arousal the systems responsible for filtering information may be impaired – the tinnitus signal may be more likely to be detected rather than filtered out. Hallam *et al.* also report work by Mandler which suggests that high levels of autonomic arousal lower the threshold of emotional responsiveness in general which facilitates orienting responses to tinnitus. It is also conceivable that high arousal levels increase sensitivity of brainstem nuclei in a similar manner to that which occurs when peripheral input is reduced. This hypothesis is supported by the work of Davis [18] who reported that the amplitude of response to sound in rats was greater following increased arousal levels.

The aims of this study were: (i) To examine the relationship between hearing threshold and psychological status; (ii) To determine whether tinnitus perception and/or reaction differed with respect to hearing status; (iii) To determine whether response to TRT differed with respect to hearing status

Methods

186 individuals referred to the former RNID MRU tinnitus over a three-year period were entered into the study. This treatment group was divided into three sub-groups on the basis of hearing thresholds:

- (1) NORM: Normal hearing (better than 20 dB HL 250 Hz to 8 kHz). N = 54.
- (2) HF: High—frequency hearing loss (better than 20 dB HL 250 Hz to 1 kHz; better than 70 dB HL 2 kHz to 8 kHz). N = 93.
- (3) MOD/SEV: Moderate to severe hearing loss (between 20 dB HL and 80 dB HL 250 Hz to 8 kHz). N = 35.

Of the original 186, 182 individuals completed five sessions of tinnitus retraining therapy (TRT) in a 12-month period. Of the remaining four, 2 died and 2 were unable to attend regularly for appointments. 159 were followed up after a further 12 months. 9 individuals were unable to attend their 24 month follow up appointment, and there was no response from the remaining 7 despite up to 2 reminder letters. Non-responders were not significantly different from responders with respect to tinnitus reaction, perception, hearing status, or response to TRT.

All hearing status groups received similar amounts of TRT directive counselling. In addition some of the NORM and HF groups were randomly assigned either just audible noise generators, noise generators set at a slightly higher level – near mixing point with tinnitus, or high-frequency emphasis hearing aids (HF group only). The MOD/SEV group received either hearing aids, or combination

instruments. Differences related to these treatments are discussed in a separate presentation (see *An Evaluation of the TRT Method*), and this paper will only examine differences related to hearing status.

At the start of the study individuals filled in a questionnaire, and audiometric investigations were carried out. The questionnaire examined tinnitus related annoyance (ANN), effect on life quality (LQ), percentage awareness(%AW) and loudness (LOUD) using interval scales from 1 to 10, and concerns about tinnitus (CONC) using a checklist of 11 common concerns. Patients were also asked to note tinnitus quality, number of sounds and location. At the first appointment individuals were asked to rate ANN, LQ and %AW “as it was when it first started”. Audiometric investigations consisted of routine pure-tone and impedance testing, tinnitus pitch-match testing, loudness discomfort level (LDL) to wide band noise, and minimum masking sensation level to wide band noise (MMSL).

The Crown Crisp Experiential Index (CCEI) [16] was used to measure anxiety, phobic anxiety, somatic anxiety, obsessionality, depression and hysteria before treatment in a representative subgroup of 118 individuals.

Patients were seen at 1, 2, 6 and 12 months post-initial consultation. They saw a medical professional and audiologist at the initial appointment, and again at 6 and 12 months. All other treatment was carried out by the audiologist. At each appointment individuals received DC, and had their instruments (where necessary) fitted and checked. After each appointment individuals filled in a questionnaire, and tinnitus pitch, MMSL and LDL were measured. Once individuals had received 12 months of TRT, they were followed up after a further 12 months (during which time they received no treatment) ie 24 months after their initial consultation.

Results

Mean hearing threshold levels for the three hearing status groups are shown in Figure 1.

Relationship between age, hearing status, and duration of tinnitus

Age and tinnitus duration increased with hearing loss. The MOD group was significantly older, and contained a significantly greater proportion of individuals who had experienced tinnitus for more than 5 years (Age: one-way ANOVA $f = 7.131$, $df = 2$, $p = 0.001$; post-hoc Tukey testing indicated MOD/SEV group were significantly different at the 0.05 level; duration: $X^2 = 30.846$, $df = 4$, $p = <0.001$). The raw data is shown in Table 1.

An assumption was made that hearing loss is likely to influence emotional status and tinnitus related reaction and perception to a greater extent than the other two factors. However it was possible that differences in age and duration of tinnitus exerted a

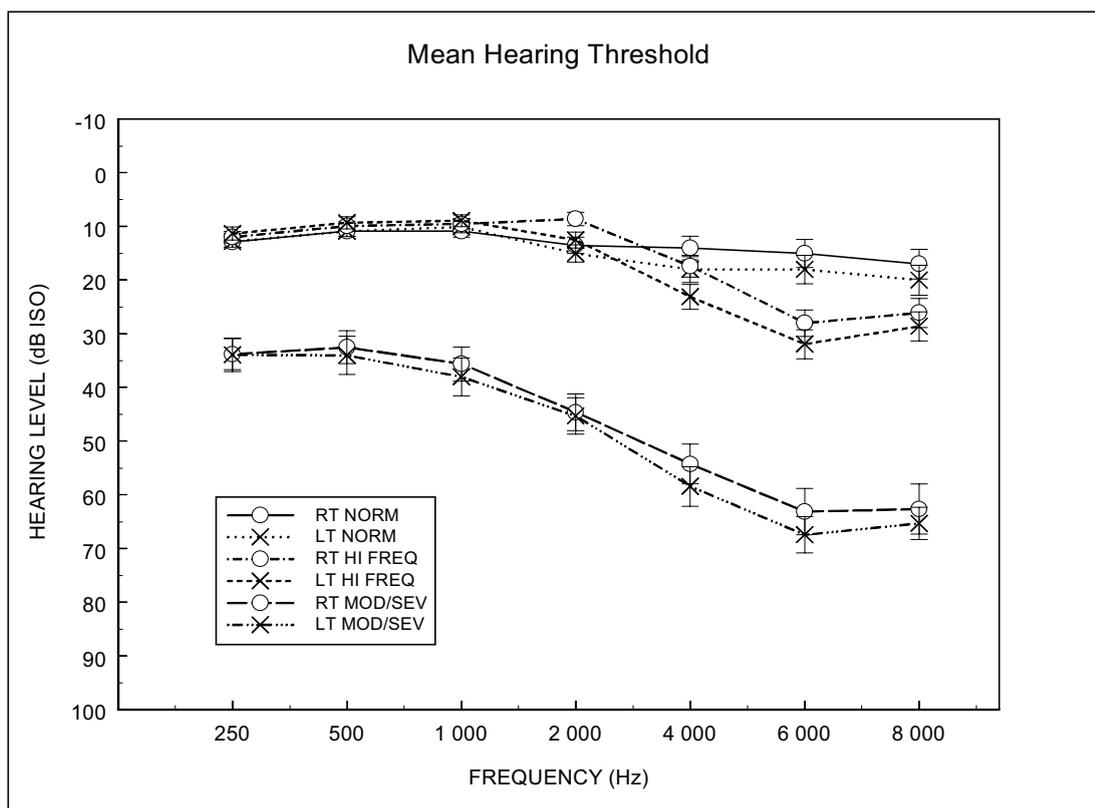


Figure 1 Mean hearing thresholds for individuals with normal hearing (NORM), mild high frequency hearing loss (HI FREQ) and moderate to severe hearing loss (MOD/SEV). Data for left (LT) and right (RT) ears are presented separately.

Table 1 Mean age, duration of tinnitus and gender for the NORM, HF and MOD groups

| Hearing status | Mean age (range) | Duration of tinnitus (% of group) | Gender (% of group) |
|----------------|------------------|---|------------------------------------|
| NORM n = 54 | 50.8 (17-81) | 35 <5 years (64.8) 12 5-10 years (22.2) 7 >10 years (13.0) | 34 male (62.9) 20 female (37.1) |
| HF n = 93 | 53.5 (19-84) | 63 <5 years (67.7) 12 5-10 years (12.9) 18 >10 years (19.4) | 56 male (60.2) 37 female (39.8) |
| MOD n = 35 | 62.2 (40-79) | 6 <5 years (17.1) 12 5-10 years (34.3) 17 >10 years (48.6) | 18 male (51.4) 17 female (48.6) |

greater influence on response to TRT than hearing status. ANOVA tests indicated that response to TRT was not significantly different for individuals who differed with respect to age or duration of tinnitus, and individuals who responded to TRT did not differ significantly from those who did not with respect to either of these factors.

Influence of hearing loss on psychological status

The 118 individuals who received the CCEI at the start of the study were not significantly different from the rest of the group with respect to age, tinnitus duration, hearing status, tinnitus characteristics or response to TRT. They were therefore

taken to be representative of the 182 individuals who received 12 months of TRT.

Results for males and females were compared separately to the age-matched normative data given by Crown and Crisp (1979) for 700 subjects from the general population. Males tended to be more dissimilar from normative values than females in general, with higher levels on all subscales with the exception of obsessionality. Females had higher levels of anxiety, phobic anxiety and depression than normal.

For males, levels of all CCEI scales except hysteria tended to increase with hearing threshold at 4000 Hz. For some reason this trend differed in females – only the phobic and somatic anxiety sub-scales increased with hearing threshold at 4000 Hz. These results are summarised in Figure 2.

Figure 2a

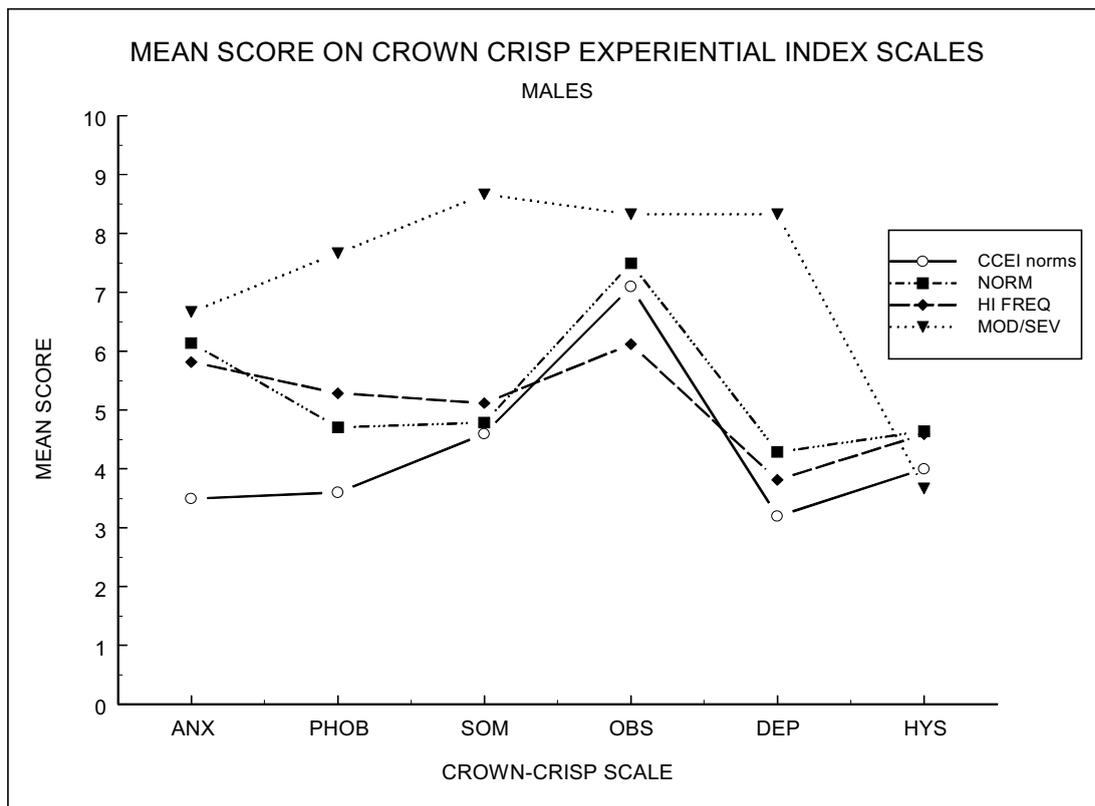


Figure 2b

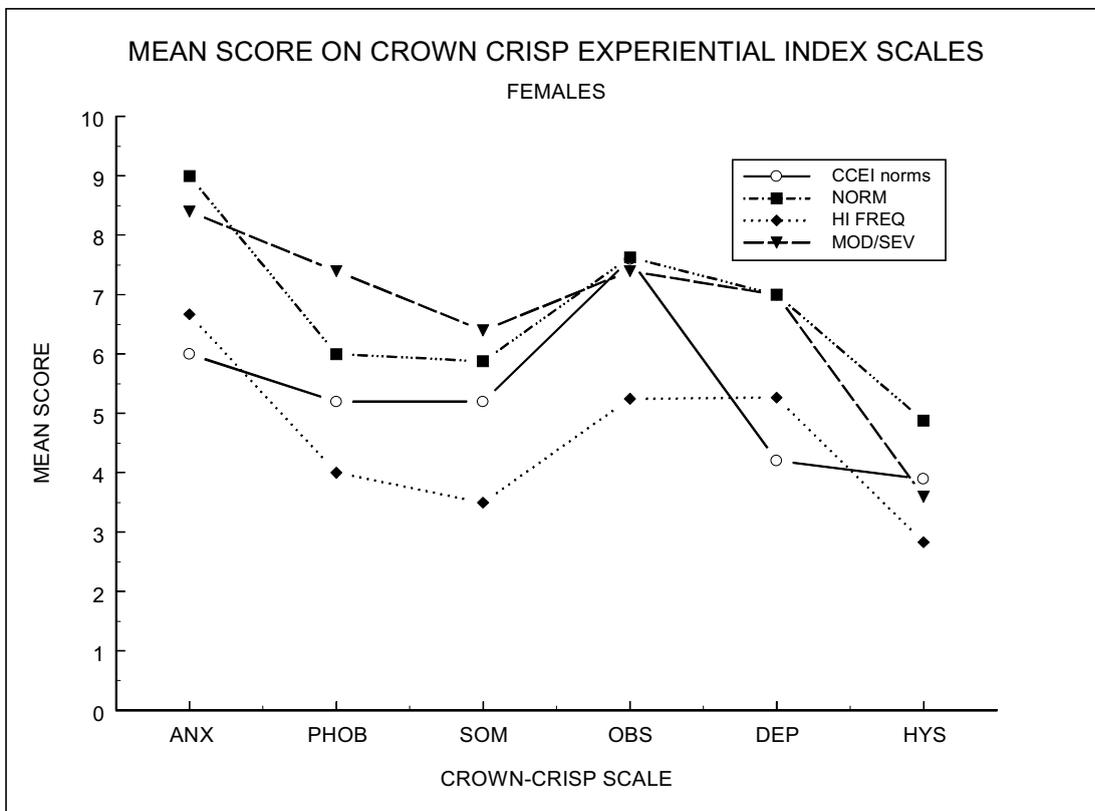


Figure 2 Normative CCEI sub—scale scores, with scores for the NORM, HF and MOD groups presented separately for males (Figure 2a) and females (Figure 2b).

Phobic anxiety in both males and females, and depression in males was positively correlated with hearing threshold at 4000 kHz (Pearson corr. co-eff. Phobia in males = 0.484, sig. at 0.01 level; Pearson corr. co-eff. Phobia in females = 0.576, sig. at 0.01 level; Pearson corr. co-eff. Depression in males = 0.458, sig. at 0.01 level).

Influence of hearing loss on tinnitus perception and reaction

Tinnitus pitch, location, quality and number of sounds

Tinnitus pitch was significantly lower for the MOD group than for the other two hearing status groups at the start of the study (NORM pitch = 5920 Hz; HI FREQ pitch = 5222 Hz; MOD pitch = 3565 Hz; Kruskal–Wallis (KW) $X^2 = 9.650, p = 0.008$). The lower pitch may have been related to the greater hearing loss in the low frequencies in the MOD group.

The majority of individuals in the study reported tinnitus in both ears (49.5%, 90), followed by right ear only (24.7%, 45) and head (16.5%, 30). Tinnitus was least commonly heard in the right ear only. The MOD group reported a greater incidence of right sided tinnitus, however Chi-square testing indicated that this was not significant. For the whole group tinnitus commonly consisted of between 1 and 3 sounds (84.1%, 153), with 2 sounds being the most common (34.6%, 63). The majority of individuals reported a “Hissing” sound (68.1%, 124). The MOD group had a significantly higher percentage of individuals who experienced more than 3 tinnitus sounds (KW $X^2 = 5.271, p = 0.072$).

These variables did not change significantly after 12 months of TRT for the whole group, however mean pitch and number of sounds decreased slightly. There were no significant differences in the amount of change between the different hearing status groups.

Minimum masking sensation level

Minimum masking sensation level (MMSL) was similar between the three hearing status groups at the start, and at the end of treatment. Levels tended to be highest for the NORM group, and lowest for the MOD group, however these differences were not significant. Changes in MMSL for all hearing status groups over the 12 month treatment period were significant. Differences between hearing status groups, or interactions between hearing status groups and time were not significant. This data with MANOVA analysis is shown in Table 2.

Loudness discomfort level to wide band noise

At the start of the study mean LDLs tended to be higher for the MOD group than the other two, however dynamic range was lower (as expected by the greater degree of hearing loss). These differences were not significant. LDLs increased significantly

Table 2 Mean MMSL for left and right ears combined at the start of the study, and after 1, 2, 6 and 12 months of TRT (ST, 1M, 2M, 6M, 12M). Standard deviations (SD) are shown for each cell. Data are presented separately for the entire treatment group (TG), and the three hearing status sub-groups. MANOVA analysis for repeated measures of time, hearing loss and hearing loss by time are shown below.

| GRP | ST | 1M | 2M | 6M | 12M |
|------|------------------|------------------|------------------|------------------|------------------|
| TG | 21.89 (17.90) | 20.21 (15.45) | 17.70 (14.55) | 16.43 (13.76) | 15.55 (15.03) |
| Norm | 24.67 (19.70) | 23.70 (18.78) | 22.39 (17.44) | 20.00 (16.67) | 20.26 (19.10) |
| HF | 21.85 (18.29) | 20.07 (13.90) | 16.41 (13.87) | 15.63 (12.68) | 14.26 (12.81) |
| Mod | 16.36 (10.60) | 13.96 (10.53) | 12.92 (6.74) | 12.31 (9.08) | 10.50 (9.85) |

| Variable | SS | DF | F | Sig. of F |
|----------------------|---------|----|------|------------|
| Hearing loss | 4342.30 | 2 | 2.80 | 0.066 (NS) |
| Time | 1706.49 | 4 | 4.85 | 0.001 |
| Hearing loss by time | 613.76 | 8 | 0.87 | 0.539 (NS) |

for all three hearing status groups over the 12 month treatment period. Differences between hearing status groups, or interactions between hearing status groups and time were not significant. This data with MANOVA analysis is shown in Table 3.

Table 3 Mean LDL (average of left and right ears) at the start of the study, and after 1, 2, 6 and 12 months of TRT (ST, 1M, 2M, 6M, 12M). SD are shown for each cell. Data are presented separately for the entire treatment group (TG), and the three hearing status sub-groups. MANOVA analysis for repeated measures of time, hearing loss and time by hearing loss are shown below.

| GRP | ST | 1M | 2M | 6M | 12M |
|------|------------------|------------------|------------------|------------------|------------------|
| TG | 88.45 (15.13) | 86.64 (16.38) | 89.53 (16.66) | 89.68 (16.11) | 93.17 (14.60) |
| NORM | 88.88 (15.39) | 88.04 (16.43) | 89.89 (15.66) | 91.79 (14.87) | 96.56 (11.72) |
| HF | 87.09 (15.39) | 84.18 (17.42) | 87.23 (18.23) | 87.85 (17.70) | 90.97 (16.86) |
| MOD | 91.33 (14.02) | 90.94 (12.21) | 95.30 (11.95) | 91.06 (13.27) | 93.71 (11.33) |

| Variable | SS | DF | F | Sig. of F |
|----------------------|---------|----|------|------------|
| Hearing loss | 585.70 | 2 | 0.42 | 0.660 (NS) |
| Time | 2324.06 | 4 | 7.70 | <0.001 |
| Hearing loss by time | 316.68 | 8 | 0.46 | 0.885 (NS) |

Questionnaire scales

Between tinnitus onset (rated retrospectively) and the start of the study median effect on life quality (LQ) and percentage awareness (%AW) became slightly lower for the entire group, however median annoyance (ANN) remained similar. Loudness (LOUD) and number of concerns about tinnitus

(CONC) were not measured during this time. There were some differences in this trend related to hearing status. Between tinnitus onset and the start of the study, levels of all three questionnaire scales had increased for the MOD group, but had decreased for the NORM and HF groups. These results are shown in Figure 3.

The MOD group rated their tinnitus at onset as better than the NORM and HF groups. However at the start of the study the MOD group rated their tinnitus as worse than the NORM and HF groups – hence levels of questionnaire scales had increased for the MOD group.

At the start of the study the MOD group tended to have more concerns, and higher levels of ANN, LQ, LOUD and %AW than the NORM and HF groups, which had similar levels. Differences in LOUD and %AW reached significance levels (LOUD KW $X^2 = 8.722$, $n = 178$, $p = 0.013$; %AW KW $X^2 = 7.895$, $n = 180$, $p = 0.019$).

Levels of CONC, EFF, ANN, LOUD and %AW remained higher for the MOD group throughout the study. At six months differences in CONC, ANN, LQ, LOUD and %AW were significantly higher (CONC KW $X^2 = 9.267$, $n = 156$, $p = 0.001$; ANN KW $X^2 = 7.149$, $n = 163$, $p = 0.028$; LQ KW $X^2 = 10.375$, $n = 155$, $p = 0.015$; LOUD KW $X^2 =$

15.840 , $n = 179$, $p = 0.004$; %AW KW $X^2 = 12.537$, $n = 177$, $p = 0.019$). At 12 months differences in ANN, LOUD and %AW were significant (ANN KW $X^2 = 6.227$, $n = 180$, $p = 0.045$; LOUD KW $X^2 = 15.628$, $n = 157$, $p < 0.001$).

However levels of all questionnaire scales became significantly lower for all hearing status groups 24 months after the start of TRT (**NORM**: CONC Friedman (F) $X^2 = 32.714$, $df = 5$, $p < 0.001$; ANN F $X^2 = 38.255$, $df = 5$, $p < 0.001$; LQ F $X^2 = 48.689$, $df = 5$, $p < 0.001$; LOUD F $X^2 = 38.839$, $df = 4$, $p < 0.001$; %AW F $X^2 = 54.663$, $df = 5$, $p < 0.001$; **HF**: CONC F $X^2 =$; CONC F $X^2 = 50.840$, $df = 5$, $p < 0.001$; ANN F $X^2 = 98.026$, $df = 5$, $p < 0.001$; LQ F $X^2 = 104.734$, $df = 5$, $p < 0.001$; LOUD F $X^2 = 59.458$, $df = 4$, $p < 0.001$; %AW F $X^2 = 94.793$, $df = 5$, $p < 0.001$); **MOD**: CONC F $X^2 = 35.244$, $df = 5$, $p < 0.001$; ANN F $X^2 = 48.448$, $df = 5$, $p < 0.001$; LQ F $X^2 = 43.703$, $df = 5$, $p < 0.001$; LOUD F $X^2 = 19.774$, $df = 4$, $p < 0.001$; %AW F $X^2 = 51.487$, $df = 5$, $p < 0.001$). Median levels of ANN, LQ, LOUD and %AW throughout the study period are shown in Figure 3.

There were no significant differences in the amount of change between different hearing status groups on any of the questionnaire scales, however

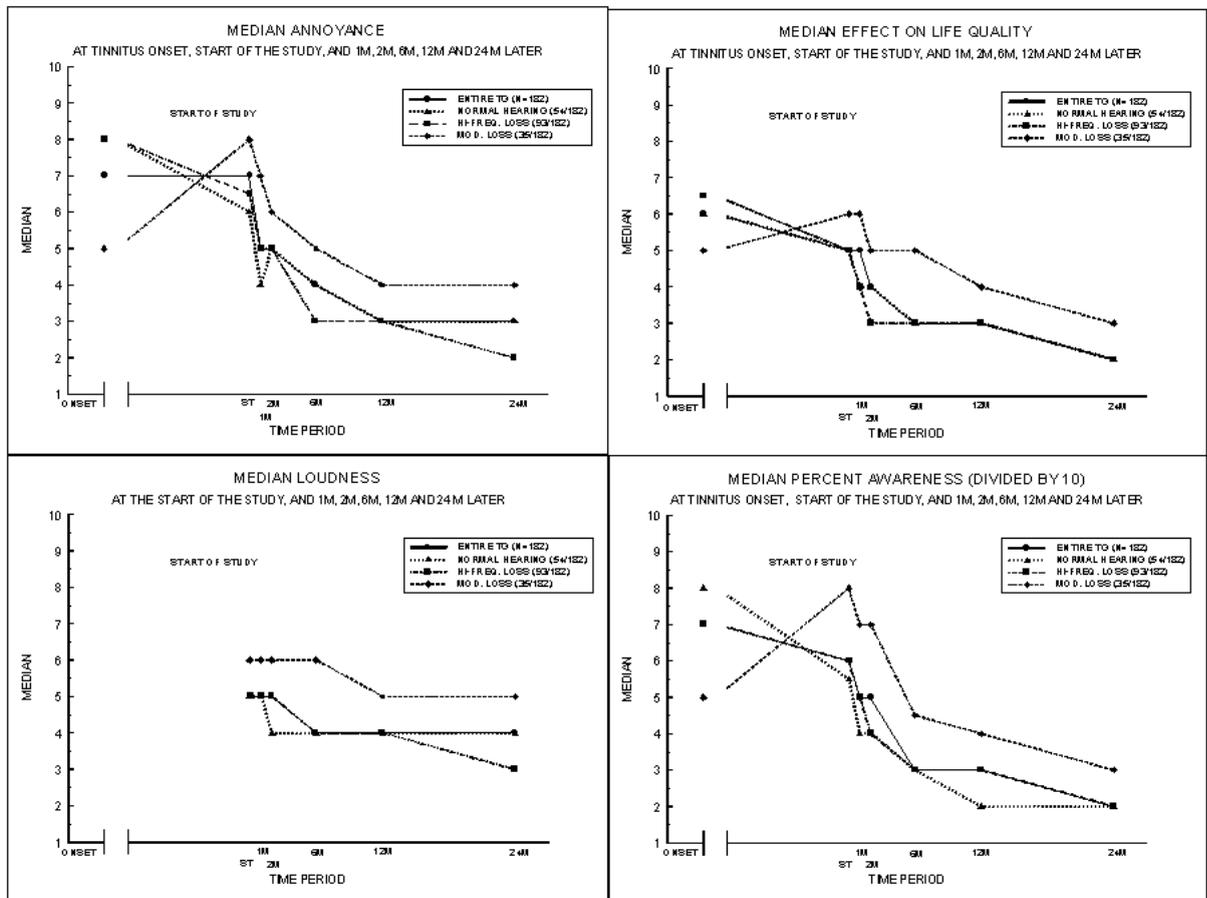


Figure 3 Median annoyance, effect on life quality, loudness and percentage awareness at tinnitus onset (rated retrospectively), at the start of the study, and 1, 2, 6, 12 and 24 months later. Medians are presented separately for the NORM, HF and MOD/SEV groups.

changes were smallest in the MOD group. Using the criteria for response to TRT of a change of 40% or greater in two or more of the questionnaire scales ANN, LQ, LOUD and %AW, 69.8% of the entire study group responded to TRT. Using the same criteria, 72.2% of the NORM group, 72.0% of the HF group, and 60.0% of the MOD/SEV group responded. This data is shown in Figure 4.

Discussion and conclusion

Hearing thresholds, age and duration of tinnitus for individuals in the NORM and HF groups were similar, whereas the MOD/SEV group had markedly lower thresholds, were significantly older and tended to have experienced tinnitus for longer. Psychological status, and tinnitus reaction, perception and response to TRT were correspondingly similar for the NORM and HF groups, but differed for the MOD/SEV group.

Greater hearing loss was associated with greater psychological disturbance. Phobic anxiety in both males and females, and depression in males were positively correlated with hearing threshold at 4000 Hz. There was also a trend amongst males for the MOD/SEV group to have higher mean scores on all CCEI scales except hysteria. It therefore appears that greater hearing loss was associated with greater anxiety, depression and obsessionality. These results are similar to those reported by McKenna

[4] who found that 27% of patients with a main complaint of hearing impairment were in need of psychological help. A higher incidence of anxiety and depression amongst individuals with tinnitus has also been reported by various other researchers [14,15,16]. It is possible that changes in emotional responsiveness and arousal associated with psychological disturbance could increase tinnitus reaction and perception [17].

In this study moderate to severe hearing loss was associated significantly lower pitch, a greater incidence of right sided tinnitus, and significantly more tinnitus sounds. Although LDL tended to be higher, dynamic range was narrower. Greater hearing loss tended to be associated with lower MMSL. These findings may be partly explained by greater sensitivity of brainstem nuclei resulting from hearing loss [9,10,11,7].

Moderate to severe hearing loss was also associated with consistently higher levels of subjectively rated tinnitus annoyance, effect on life quality, loudness and percentage awareness throughout the 24 month study. However hearing loss did not appear to influence response to TRT significantly, even though 12% fewer of the MOD/SEV group compared to the NORM and HF groups responded significantly to 12 months of TRT.

Individuals with a greater degree of hearing loss had shown less habituation to tinnitus before the study than individuals with either normal hearing or a mild degree of hearing loss. This observation suggests that even if hearing loss and its associated

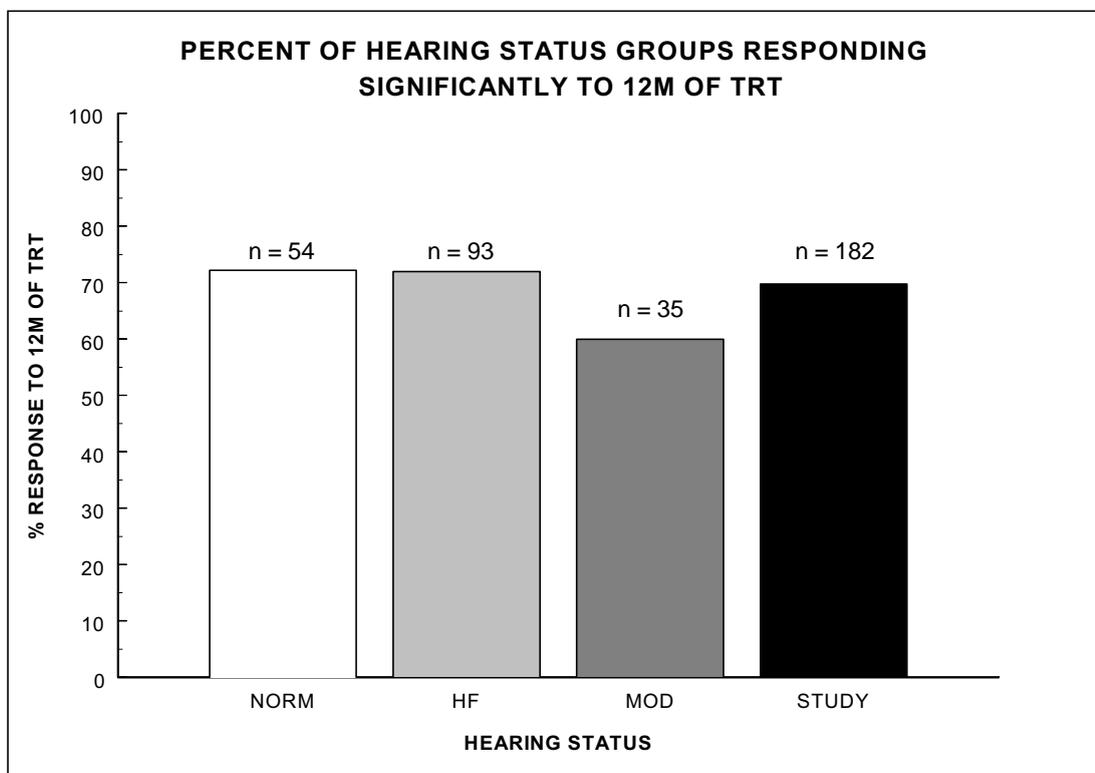


Figure 4 Percent of hearing status groups who responded significantly to 12 months of TRT. The same data is shown for the entire study (STUDY) for comparison.

factors did not influence response to TRT during the study period, these factors may have some influence on spontaneous habituation over a longer period of time. Patients who reported that their tinnitus had been worsening may have in fact been reporting the effects of their hearing loss. Hazell has suggested that increases in emotional stress and arousal resulting from "straining to hear" lead to greater tinnitus perception and reaction.

In this study only 19.2% of individuals had a moderate to severe hearing loss. This suggests that for the majority of individuals referred to the tinnitus clinic factors other than hearing loss caused them to seek help, however for those with hearing loss it increased tinnitus-related distress. Once hearing loss was properly rehabilitated however, it did not significantly affect response to TRT.

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Our experience in treatment of patients with tinnitus and/or hyperacusis using the habituation method

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Habituation known also as Tinnitus Retraining Therapy (TRT) is an efficacious therapeutic method in treatment of patients with tinnitus and/or hyperacusis. TRT offers possible relief for tinnitus sufferers by habituation of the negative emotion induced by tinnitus and habituation of tinnitus perception. In The Tinnitus and Hyperacusis Management Clinic at the Institute of Physiology and Pathology of Hearing in Warsaw for over 2 years the treatment of patients is based on a neurophysiological model of tinnitus.

One hundred and twenty cases were evaluated out of 556 patients registered till March 1999 at our Clinic. There was no patient preselection, except the requirement that the patients had to be treated for at least 12 months. The complete therapy takes 18 to 24 months. All patients received counselling and were advised of using sound according to a specific protocol. After that, all of them had a number of follow-up visits depending on individual needs. The 120 patients were investigated in 5 categories, 24 patients in each category. A special questionnaire, administered before and during the treatment (when our data were collected) was used to assess the results. Patients had to indicate the impact of tinnitus on their life, degree of annoyance, tinnitus severity and percentage of time they are aware of tinnitus on the scale of 0 to 10. They were also asked about activities that had been disturbed by their tinnitus and/or hyperacusis.

Significant improvement means that at least one activity has stopped being affected by tinnitus and the patient enjoy at least 20% improvement in at least three measures.

After minimum 12 months of therapy in the group of 120 subjects the results of therapy differ in each category but they show significant improvement in almost 80% of the cases. Despite good initial effects the treatment should be continued for 18–24 months. Our data are promising therefore we can expect more successful results at the end of treatment. It would confirm the effectiveness of this method in Poland.

Introduction

At present there are many centres in the world treating patients with tinnitus. They offer various methods of treatment. However, no 100% effective method of treatment nor cure for subjective tinnitus has been found yet. The habituation method, known also as TRT (Tinnitus Retraining Therapy) elaborated in the mid eighties by professor Pawel Jastreboff from University of Maryland (USA) is considered very useful therapeutic method [1,2,3]. It is based on the so-called neurophysiological model of tinnitus origin [4]. It points out that various centres of the brain are involved in tinnitus emergence and it is focused basically on suppressing negative reactions and associations caused by

tinnitus as well as suppressing or even eliminating its perception in the cerebral cortex [2]. These effects can be achieved owing to the plasticity of the brain and its ability to filter certain signals. The habituation of reactions takes place by means of gradual decrease in stimulation level from the cortical areas to the limbic and autonomic system. This is achieved during one directive counselling and a series of individual counselling, the number of which depends on the individual needs of the patient. Habituation of perception takes place as a result of decreasing the level of stimulation from the auditory subcortical centres. It is achieved by means of sound therapy, using various acoustic backgrounds, wideband noise generators or hearing aids.

Patients with tinnitus and/or hyperacusis are divided into 5 therapeutically categories. In each category different variants of counselling and sound therapy are used. The full period of treatment by habituation method is from 18 to 24 months and,

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according to world-wide data, is successful in 80% of cases [1,3].

At The Tinnitus and Hyperacusis Management Clinic of the Institute of Physiology and Pathology of Hearing in Warsaw, we have dealt with patients suffering from tinnitus and/or hyperacusis using TRT method on the large scale for over two years. In our treatment we strictly apply all the procedures regarding specific protocol which is helpful in habituation.

Aims

The aim of this work was to summarise the results of habituation of our patients after minimum 12 months of therapy, taking into consideration the category of treatment.

Material

The material of these work comprised 120 cases [68 women, 52 men] evaluated out of 556 patients registered till March 1999 at our Clinic. From each therapeutically category we have randomly chosen 24 patients for whom the only criterion of selection was the time period of therapy. The patients have been treated with the full protocol for at least 12 month and not longer than 18 months.

In Table 1 selection criteria to appropriate categories of treatment are presented.

Method

Based on the experience of world leading centres [3,5] which were the first to introduce the habituation method into treatment and also our own few-year-long experience, a protocol of treatment of patients with tinnitus and/or hyperacusis obligatory at the Tinnitus and Hyperacusis Management Clinic was established.

The protocol includes [2,6,7]:

- case history, filling in the initial contact questionnaire

- audiological evaluation
- medical evaluation
- diagnosis and selection for the treatment category
- directive counseling
- selection and fitting of the most suitable hearing aids or noise generators
- follow-up counseling according to the individual needs of the patient and established timetable.

To evaluate the effects of treatment a special questionnaire was elaborated based on the one proposed by Margaret and Pawel Jastreboff. It comprises the following parameters, which are presented in the form of questions to be answered by patients before, during and after the treatment:

- the impact of tinnitus and hyperacusis on various everyday life activities
- percentage of time of being awake during which they are aware of tinnitus
- the degree of annoyance evaluated by the patient on the scale from 0 to 10
- the impact of tinnitus and/or hyperacusis on the life of the patient on the scale from 0 to 10
- the intensity of tinnitus on the scale from 0 to 10
- intensification of tinnitus after exposure to loud sounds and duration.

The measurement of uncomfortable loudness level (UCL) is also repeated during and after the treatment.

Comparing the data acquired from the questionnaire the pre-, inter-, and post-therapy results of the effects of treatment were evaluated by means of two criteria: significant improvement and no improvement or deterioration.

The criterion of significant improvement was the decrease of at least three of the above mentioned parameters by a minimum of 20% and the liberation of at least one of the everyday life activities previously impaired by tinnitus and/or hyperacusis.

For statistical analysis of the results Chi Square Test was employed.

Table 1 Selection criteria to appropriate categories of treatment.

| Category of treatment | Hyperacusis | Noise exposure | Subjective hearing loss | Treatment |
|-----------------------|-------------|----------------------|---------------------------|--|
| Cat. 0 | absent | no prolonged effect* | irrelevant | counselling only; avoid silence |
| Cat. I | absent | no prolonged effect | irrelevant | noise generators set at level close to "mixing point" |
| Cat. II | absent | no prolonged effect | significant | environmental sounds amplified by hearing aids |
| Cat. III | present | no prolonged effect | irrelevant or significant | noise generators set close to threshold of hearing with the sound level gradually increased during the treatment |
| Cat. IV | present | present | irrelevant or significant | noise generators set at threshold with the level gradually increased during the treatment |

* prolonged effect means: prolonged (min. for several hours) enhancement of tinnitus and/or hyperacusis as a result of noise exposure

Table 2 Results of habituation

| | Categories | Significant improvement | No improvement |
|-----------------------------|-------------------|-------------------------|------------------|
| Number of patients n=120 | Category 0 n=24 | 22 patients (92%) | 2 patients (8%) |
| | Category I n=24 | 20 patients (83%) | 4 patients (17%) |
| | Category II n=24 | 17 patients (71%) | 7 patients (29%) |
| | Category III n=24 | 18 patients (75%) | 6 patients (25%) |
| | Category IV n=24 | 16 patients (67%) | 8 patients (33%) |
| | | Average: 77,6% | Average: 22,4% |

Results

Results of habituation are presented in Table 2

Considering particular therapeutically categories statistically significant differences have only occurred between: cat. 0 and cat. IV [$p < 0.05$].

Discussion and conclusions

The results of our studies on the effectiveness of habituation in treatment of tinnitus and/or hyperacusis are very promising and similar to those reported by other authors [2,3,5]. Our data were collected after minimum 12 months from the beginning of training. TRT appears to be a successful therapy but it requires 18-to-24 months of treatment [3,4]. As it basically involves changes in neuronal connections in the auditory system, it usually cannot be achieved quickly. Thus when duration of treatment increases, the percentage of patients with significant improvement should grow. So after completed period of therapy larger success can be expected.

The data from our investigated group show also the dependence of results of therapy on therapeutically category of treatment (particularly between cat. 0 and cat. IV). The greatest percentage of significant improvement has been obtained in category 0 what agreed with reports from other word centres [3,5]. In a few patients from that group, significant improvement was noted after the first, directive counselling. TRT was less effective for patients from category IV. The majority of them first have reported improvement in hyperacusis than in tinnitus. Our data suggest also that the type of device used has no significant impact on the treatment outcome as earlier was reported by Jastreboff [8]. Proving the impact of duration on efficiency of treatment needs more time and research on a larger number of patients.

Further detailed analysis of clinical results on a larger material will allow for more precise assessment of the effectiveness of habituation with Polish

patients, as well as comparing it with the efficiency achieved in other centres in the world.

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The audiological profile of tinnitus in elderly Australians: Preliminary findings

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The audiological characteristics of people with tinnitus have been used as evidence for theories on the generation and maintenance of tinnitus. However, such data have tended to come from people attending tinnitus clinics who suffer from more severe tinnitus than those who do not experience any annoyance due to tinnitus. The audiological profile, consisting of measures of pure tone audiometry and otoacoustic emissions, was examined in a sample of 996 elderly people aged between 54 and 94 years of age from the Blue Mountains Hearing Study. These measures were compared between groups with and without tinnitus as well as between different levels of tinnitus type and severity within the tinnitus group. The tinnitus group demonstrated worse results on average than the non-tinnitus group for all audiological measures. The average differences between the tinnitus and non-tinnitus groups were greater for measures of pure tone audiometry than for OAEs. These results clearly indicate a strong association between damage to the peripheral auditory mechanism and the generation of tinnitus. However, there were no significant differences in any average audiological measures between groups reporting different degrees of tinnitus annoyance. Thus it would seem that damage to the peripheral auditory mechanism is of secondary importance in determining level of annoyance due to tinnitus and this is consistent with the neurophysiological model of tinnitus.

Introduction

Overview of the blue mountains hearing study

The Blue Mountains Hearing Study (BMHS) is a population based survey of age related hearing loss in an older Australian community. The BMHS commenced in June 1997 and is still in progress. The BMHS has been carried out in conjunction with an eye study (BMES-2) which has been a follow up study to an initial eye study (BMES-1). In this first eye study, 3654 people aged 49 to 97 were examined during 1992–4, following a door to door census of 38 census districts in 2 postcode areas of the Blue Mountains which are west of Sydney. After excluding people who died or left the area during the survey, the response rate was 88% of the permanent residents counted during the census. Each participant of BMES-1 was requested to participate in both the follow up eye study (BMES-2) and the

hearing study (BMHS). The population surveyed in the BMES was considered, on the basis of analysis of the census data, to be similar in demographic characteristics, such as ethnic and socioeconomic distribution, to the broader Australian community.

Each subject in the BMHS was examined by an audiologist using a comprehensive questionnaire and measurements of hearing, middle ear and cochlear status and central auditory functioning. This presentation analyses and compares the audiological data (measures of pure tone audiometry and otoacoustic emissions) and tinnitus data from the examination of the first 996 subjects in the BMHS.

Methodological advantages of the BMHS in tinnitus research

The BMHS is uniquely placed to provide quality data on the audiological profile of people with tinnitus for the following reasons:

Comprehensive sampling: As mentioned previously, the BMES-1 had a very high response rate from test subjects. At the time of writing, the response rate to the BMHS continued to be high

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(over 75%) and this was before any attempts had been made to follow up non-respondents and to make alternative testing arrangements if it was difficult for the subjects to attend the main testing site. As a result, the audiological profile of people with tinnitus in the BMHS is much more likely to be representative of the total population of people with all manifestations of tinnitus rather than a potentially biased sample. For example, many studies that have carried out audiometric testing and/or examinations of otoacoustic emissions (OAEs) on people with tinnitus [1,2,3,4] have used people who were attending tinnitus clinics or tinnitus *sufferers* as the subjects for research. It is also interesting to note that the neurophysiological model of tinnitus arose from observations of tinnitus sufferers made in such tinnitus clinics [5,6]. Thus, while these researchers have found no significant correlations *within* groups of tinnitus sufferers between audiometric measures and degree of suffering caused by tinnitus, this would not necessarily rule out the presence of significant differences of average audiometric results *between* groups that are annoyed by tinnitus and those that are not. Therefore, the BMHS allows the detailed examination and comparison of the characteristics of a group that has probably been overlooked by most hearing care providers, that is, people who experience tinnitus but are not annoyed by it.

Inclusion of otoacoustic emissions: The BMHS is the first epidemiological study of hearing to use measurement of transiently evoked otoacoustic emissions (TEOAEs) and spontaneous otoacoustic emissions (SOAEs) as part of its assessment battery. This enables an additional measurement of the integrity of the peripheral auditory mechanism which can then be compared with measures of tinnitus prevalence and annoyance. It should be noted that a similar epidemiological study of hearing has been carried out in Beaver Dam, Wisconsin in the USA [7]. This study has many similarities to the BMHS in that it examined the hearing of 3753 people 48–92 years of age as part of a follow up to an original eye study five years previously. The Beaver Dam study included questions about tinnitus as well as measures of pure tone audiometry and distortion product OAEs. Although at the time of writing there was no information from this study in press relating tinnitus to hearing threshold and OAE test results, it is hoped that data from both studies may be pooled across continents, as has been the case already for some of the eye data.

It seemed reasonable to propose that by examining the audiological profile of people with tinnitus, the validity of models of tinnitus generation might also be examined. This was achieved both by comparing the audiological profile of people with tinnitus to that of people without tinnitus and by examining the profile of people with differing levels of tinnitus annoyance. Hence, it was proposed that if there was a significant difference in the audiological profile (in terms of average pure tone audiometry thresholds and strength of otoacoustic emissions) between the group of people with tinnitus and the

group without tinnitus, then this would point to an important role for the peripheral auditory mechanism in the generation of tinnitus. In addition, if significant differences were found in the audiological profile between groups with differing levels of tinnitus annoyance, then this would tend to point towards a more important role of the peripheral auditory system in determining levels of tinnitus annoyance. If, however, there were no significant differences in any of the audiological measures between these groups, then this finding would tend to suggest that tinnitus annoyance is not influenced by the extent of peripheral auditory pathology and thus provide support for the neurophysiological model of tinnitus generation.

Summary and aims of research

Apart from a few studies on small numbers of subjects that found an exclusively retrocochlear origin to tinnitus [8,9], there is little contention in the literature as a whole that tinnitus is associated with peripheral hearing loss. It seemed likely that when the audiological profile of subjects with tinnitus was examined in large numbers, the group with tinnitus would have, on average, worse hearing and cochlear function than the group without tinnitus. What remained unclear was whether there would be any link between level of damage to the peripheral hearing mechanism and level of tinnitus annoyance. For example, using audiological and tinnitus data from the National Study of Hearing (NSH) in the UK, a trend was found for greater levels of annoyance caused by tinnitus to be associated with greater levels of hearing loss [10]. However, others [1] have found no correlation between level of tinnitus annoyance and audiological measures.

The main aims of this research were therefore to determine if there was any significant audiological difference (as measured by pure tone audiometry and measures of otoacoustic emissions) between:

- (1) subjects who experience tinnitus and subjects who do not experience tinnitus;
- (2) subjects who experience high levels of annoyance due to tinnitus and subjects who experience little or no annoyance due to tinnitus.

Methods

The tinnitus data from the BMHS questionnaire and the data from testing of pure tone audiometry and OAEs from a total of 996 people from the BMHS were examined. All subjects were aged between 54 and 94 years of age with the average age being 69.2. Each subject was examined at the Blue Mountains Hospital between July 1997 and November 1998. Audiometric testing was performed using a Madsen OB 822 audiometer. OAE testing was performed using an Otodynamics Echoport ILO288 otoacoustic emission analyzer with version 4.2OB software running on a Toshiba 440 CDX laptop computer. The ATA Survey from Portland Oregon was included in the questionnaire

as the basis for questions on tinnitus. The definition of tinnitus used by the BMHS was “have you experienced **any** prolonged ringing, buzzing, or other sounds in your ears or head within the past year . . . that is, lasting for 5 minutes or longer”. At the beginning of the BMHS, the tinnitus questionnaire had a slightly different format. Questions concerning when tinnitus was present, i.e. occasionally, often or all the time, were coded differently to the current questionnaire format. As a result, any analyses using the variable of when tinnitus was present were restricted to a sample of 730 subjects who were examined with the current questionnaire.

Four audiometric variables were created from the pure tone audiometry hearing thresholds data at different frequencies:

- Four frequency average (4FA) for the better and worse ears for each subject. 4FA was the average of the hearing thresholds at 500, 1000, 2000 and 4000 Hz.
- High frequency average (HFA) for the better and worse ears for each subject. HFA was the average of the hearing thresholds at 4000, 6000 and 8000 Hz.

Five OAE variables were created from the raw OAEs data. The first two variables were the overall waveform reproducibility between adjacent responses (WAVEREPRO%) for the better and worse ears. WAVEREPRO% is a result parameter from the Otodynamics Echoport ILO288 otoacoustic emission analyzer that is considered to be a net measure of the overall strength of TEOAEs across the test frequency range [11]. The next two variables obtained were the WAYERPRO% for the better and worse ears in the 4 kHz TEOAE band. It was considered that some measures of high frequency OAEs were needed in case high overall WAVEREPRO% among subjects with tinnitus was due to strong low frequency OAEs. Other research [4] has found that high frequency OAEs differentiated normal hearers with and without tinnitus. The final OAE variable obtained was whether SOAEs were present or not in one or both ears for a given subject. SOAEs were judged as being present when the amplitude of the SOAE was 10 dB or greater above the noise floor. Only a single measurement of an SOAE at any frequency was necessary for a subject to be recorded as having SOAEs present.

All statistical analyses were performed using an SPSS statistical software package. The results from these analyses are presented in the following section.

Results

Prevalence

The prevalence of tinnitus of any sort that lasted more than five minutes in this sample of 996 subjects was found to be 30.9%. Around 50% of people experiencing tinnitus reported mild annoyance whereas only 12.6% reported that their tinnitus was very annoying and only approximately 3% reported that their tinnitus was extremely annoying. Thus, just fewer than 5% of the entire sample of 996 subjects reported having tinnitus that was either very or extremely annoying. From the subset of 730 subjects who were questioned with the most recent version of the tinnitus questionnaire, 10.8% of people reported hearing tinnitus only occasionally, 6.4% reported hearing tinnitus often and 11.1% reported hearing tinnitus all the time. Only four subjects were unsure how often they experienced tinnitus.

Comparison of audiological profiles between tinnitus and non-tinnitus groups

In Table 1 the audiometric and OAE data can be compared between people with no tinnitus and people who experienced tinnitus of any type. The tinnitus group demonstrated higher mean hearing thresholds for measures of 4FA and HFA in both the better and worse ears. These mean differences were then analysed using t-tests for equality of means and were found to be significant ($p = 0.01$) for the 4FA results in the better ear. Mean differences were significant ($p < 0.001$) for the 4FA results for the worse ear and the HFA results for the better and worse ears. The mean overall WAVEREPRO% was also worse, i.e. lower, in the tinnitus group. However, the differences between tinnitus and non-tinnitus groups for overall WAVEREPRO% in the better and worse ears were not as significant ($p = 0.05$) compared to the differences in pure tone audiometry measures. Furthermore, in a subgroup of subjects with close to normal hearing (4FA thresholds ≤ 20 dBHL), there were no significant differences in either average overall WAVEREPRO% or average WAYERPRO% in the 4 kHz band between subjects with and without tinnitus.

The audiological profile of the subset of 730 subjects was examined. The people with tinnitus in this subset were questioned when their tinnitus was present and were then divided into three groups –

Table 1 Comparison of mean audiological results between people with and without tinnitus

| | Better ear 4FA dBHL | Worse ear 4FA dBHL | Better ear HFA dBHL | Worse ear HFA dBHL | Better ear WAVEREPRO% | Worse ear WAVEREPRO% |
|------------------------------------|------------------------|-----------------------|------------------------|-----------------------|--------------------------|-------------------------|
| Non-tinnitus group (n = 688) | 22.33** | 28.22*** | 43.15*** | 52.05*** | 65.62* | 46.86* |
| Tinnitus group (n = 308) | 24.84.** | 32.83*** | 49.49*** | 59.15*** | 61.81* | 42.29* |

8 $p = 0.005$; ** $p = 0.01$; *** $p = 0.001$

those who reported experiencing tinnitus only occasionally, often and all the time. People who reported experiencing tinnitus occasionally and often had, on average, worse hearing thresholds than people without tinnitus ($p = 0.05$ for HFA measures in the better ear and $p < 0.1$ for HFA measures in the worse ear). In turn, people who experienced tinnitus all the time generally had worse average hearing thresholds than people with tinnitus occasionally and often ($p < 0.1$ and $p = 0.05$ for 4FA and HFA measures respectively in the worse ear). Although average WEVEREPRO% measures were worse for the tinnitus group as a whole compared to the non-tinnitus group, there was no consistent trend for WEVEREPRO% measures to decrease with increasing prevalence of tinnitus being heard.

Other links between hearing loss and tinnitus were also found in these data. A greater proportion of tinnitus was heard in the left ear alone (17% of tinnitus group) than in the right ear alone (10%). Similarly, when tinnitus was heard bilaterally, a larger proportion of tinnitus was reported as being louder in the left ear (10.5%) than louder in the right ear (6.9%). For measures of 4FA and HFA, hearing thresholds were worse, on average, in the left ear and this difference was found to be significant ($p < 0.001$). Thus, the greater prevalence of tinnitus in the left ear is possibly a result of worse average hearing thresholds in the left ear.

Comparison of audiological profiles within the tinnitus group

A One Way Analysis of Variance (ANOVA) was carried out on each of the audiometric and OAE variables (4FA, HFA and overall WEVEREPRO% measures for the better and worse ears) to compare them between different categories of tinnitus annoyance. Results from the ANOVA indicated that there were *no significant differences* for any of these variables between the different groups of annoyance caused by tinnitus. However, around 60% of people who reported very and extremely annoying tinnitus annoyance also reported experiencing tinnitus all the time. This was a significantly greater proportion ($p < 0.05$) than the 34.3% of people with tinnitus that was mildly annoying or not annoying at all, who reported experiencing tinnitus all the time. Hence the milder the tinnitus annoyance, the less likely people would report hearing tinnitus all the time.

Table 2 demonstrates the prevalence of SOAEs amongst the different categories of tinnitus annoyance. Due to the small numbers in the very and extremely annoying categories, a Chi-Square Test

was performed combining these two categories to compare the prevalence of SOAEs in the combined very and extremely annoying categories with the prevalence of SOAEs in the mildly and not annoying at all categories. A significantly greater proportion ($p < 0.05$) of people with very and extremely annoying tinnitus had SOAEs in one or both ears than people with tinnitus that was only mildly annoying or not annoying at all.

Discussion

When the audiological data concerning people with tinnitus are considered, it is quite clear that hearing, on average, is worse in both the lower and higher frequencies than for people without tinnitus. However, while people with tinnitus *as a group* have hearing that is worse than people without tinnitus, there were people in each tinnitus group (either according to annoyance or prevalence category) who did not seem to have any damage to their hearing mechanism that could be measured by pure tone audiometry thresholds.

The finding of tinnitus being present in people with normal hearing thresholds is not a new one [1]. It was hoped that the use of WEVEREPRO% measures in this study might provide an objective measure that differentiated people with and without tinnitus who had close to normal hearing. WEVEREPRO% values as low as 35% have been associated with normal hearing thresholds [12]. However, these results have indicated that WEVEREPRO% measures (both overall and in the 4 kHz band) are no more associated with the presence of tinnitus than are measures of hearing threshold. Differences in the amplitude of DPOAEs in the high frequency region of 4–7 kHz have been reported to differentiate tinnitus and non-tinnitus groups with normal hearing [4]. Since TEOAE recordings only measure OAEs up to around 5 kHz, it may be that TEOAE testing does not allow assessment of outer hair cell function in frequency regions that might differentiate tinnitus and non-tinnitus groups with normal hearing. It is also important to note that not all studies in the literature agree with the premise that OAEs can provide early indication of cochlear damage prior to a measurable hearing loss and hence, by implication, an indication of early tinnitus causing cochlear damage [13].

Although the link between hearing loss and the presence of tinnitus is clear from these data, there does not seem to be any link between either measures of hearing threshold or TEOAEs and level of annoyance caused by tinnitus. Thus, the finding from the results of the NSH of a tendency for greater degrees of hearing loss to be associated with greater levels of tinnitus severity [10], does not seem to be supported by these results. These results would tend to suggest that something other than the status of the peripheral hearing mechanism is responsible for levels of tinnitus annoyance and are consistent with the neurophysiological model of tinnitus, which stresses the dominance of non-

Table 2 SOAE prevalence in different annoyance categories

| Tinnitus annoyance category | N | Percentage of subjects with SOAEs in one or both ears |
|-----------------------------|-----|---|
| Extremely annoying | 9 | 56% |
| Very annoying | 38 | 45% |
| Mildly annoying | 148 | 29% |
| Not annoying at all | 98 | 28% |

auditory systems in determining the level of tinnitus annoyance.

This apparent contradiction in findings may be due to variations in definition of tinnitus. The NSH defined tinnitus as noises in the head or ears that lasted more than five minutes and were not immediately after exposure to loud sounds. This definition was also referred to as "prolonged spontaneous tinnitus" (PST). The BMHS kept the requirement that tinnitus should last more than five minutes but did not exclude tinnitus that occurred after loud sounds and hence the BMHS data on tinnitus could be said to describe "prolonged tinnitus" (PT). This broader definition of tinnitus may account for the higher prevalence figure (30.9%), even when compared to the NSH prevalence of PST (16%) for adults in the 61–70 age group, which was the age group with the highest PST prevalence [14]. It also seems possible that there may be a link between extent of hearing loss and level of annoyance due to PST but no link between hearing loss and level of annoyance due to PT.

The result that people with very and extremely annoying tinnitus are more likely to report experiencing tinnitus all the time might be interpreted in two ways. Firstly, it might be possible that tinnitus that is heard all the time is intrinsically more annoying than tinnitus that is heard often or only occasionally. Alternatively, this result might be explained by the neurophysiological model that would suggest that a sound that is perceived as a threat or with negative associations is also more likely to be consciously attended to and hence perceived as being heard all the time. Given that for all other measures (other than prevalence of SOAEs which is discussed below) the very and extremely annoyed groups were indistinguishable from the mildly and not annoyed groups, it would seem that this second explanation is more likely.

The only audiological results that seem to have any link with level of tinnitus annoyance are the SOAE results. If very annoying or worse tinnitus was the result of worse damage to the peripheral hearing mechanism then the expected result might have been a lower prevalence of SOAEs than for the mildly annoyed and not annoyed groups, but it seems that the reverse result is true. A possible explanation for this result might be found in the neurophysiological theory of tinnitus, which suggests that people who have very annoying tinnitus have enhanced detection of the tinnitus signal due to perceptions that the sound is a threat [5]. As a result, the efferent pathways to the cochlea that are thought to be able to enhance the ability to listen to very soft sounds by "tuning" the basilar membrane may be in a state of constant activation as the person with very annoying tinnitus constantly attempts (although unwillingly) to listen to a "threatening" sound. Thus SOAEs in the very and extremely annoyed tinnitus groups may be a result of enhanced tuning of the basilar membrane and hence SOAEs may be a *result* rather than a *cause* of very and extremely annoying tinnitus.

Conclusions

The tinnitus and audiological data from the BMHS are at this stage incomplete. However, from this sample of 996 subjects a number of clear trends have emerged. Firstly, it has been demonstrated that tinnitus would seem to be associated with damage to the peripheral auditory mechanism since people with tinnitus, as a group, had worse measures of pure tone audiometry and OAEs. Secondly, there is within the tinnitus group, a trend for people who experience tinnitus all the time to demonstrate more damage to the peripheral auditory mechanism as measured by pure tone audiometry and OAEs than for those who experience tinnitus occasionally. There is, however, no evidence of any association between level of tinnitus annoyance and the amount of damage to the peripheral auditory mechanism. These results suggest that while the generation of tinnitus seems to be strongly linked with damage to the cochlea (only 6.1% of the entire sample had conductive or mixed hearing losses in either ear), the extent of cochlear damage or the strength of the cochlear tinnitus generator would appear to be of secondary importance in determining the level of annoyance due to tinnitus. Thus it would seem that these results lend support to the neurophysiological theory of tinnitus.

Future research

The neurophysiological theory of tinnitus has not so much been supported by evidence from this study but rather has been supported by the absence of evidence that might contradict this theory. That is to say it has been the *lack* of any significant link between impairment to the hearing mechanism and level of tinnitus annoyance that have suggested non-psychoacoustical mechanisms responsible for degree of tinnitus distress. There is, however, information from the BMHS questionnaire concerning hearing aid use amongst the BMHS subjects. It would be interesting to see if further research will find whether the prediction made by the neurophysiological theory that use of hearing aids can reduce the level of tinnitus annoyance by reducing the "straining to hear" phenomenon is supported by these data.

Finally, the role of OAEs in tinnitus needs further investigation. In particular, more OAE parameters beyond WEVEREPRO%, such as amplitude and bandwidth of response, need to be examined to see if OAEs can provide any indication of cochlear damage in normally hearing people with tinnitus. Furthermore, the characteristics of SOAEs in people with tinnitus need more detailed analysis. For example, the amplitude, frequency and number of SOAEs could be compared between people with and without tinnitus and between people with different degrees of tinnitus annoyance. Also, further investigation is needed into the characteristics of SOAEs in people with very and extremely annoying tinnitus to determine if attention has any influence on the various SOAE parameters for this group.

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Relationships between tinnitus loudness and severity

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Epidemiological data from the UK National Study of Hearing [1,2] shows a strong relationship between prevalence of tinnitus and threshold of hearing at high frequencies. However, loudness data are confounded by the problem of recruitment, which means that sensation level units often under-rate the loudness, and hearing level units over-rate it. These can be overcome by using the nomogram of Matsuhira *et al* [3]: using hearing threshold and tinnitus loudness match levels, the absolute loudness in units of Effective Loudness Level (ELL) can be estimated. This is the loudness of an audiometric tone at that hearing level as heard by a normally-hearing person. Data presented at the Fifth International Tinnitus Seminar indicated the ELLs of people with tinnitus in the UK and Japan to be in the region of 0 to 70 dB HL with an average of 15–21 dB HL [4,5].

The present paper extends our previous study to study the relationships between ELL and degree of tinnitus distress and also the threshold of hearing. We found no statistical correlation at all between ELL and degree of distress or hearing threshold, but there was a weak correlation between hearing threshold and tinnitus loudness. From this, we conclude that a tinnitus loudness measurement is unhelpful as an indicator of tinnitus severity, unless it is one of a series of measurements monitoring changes. Our findings also seem to fit in well with the general concepts in Jastreboff's neurophysiological theory of tinnitus [6].

Introduction

In the last decade there has been a shift of emphasis from the “otocentric” concept of tinnitus and its treatment, to one which places great importance on the brain both in detection of the tinnitus-related neuronal signal and in generation of distress. Nevertheless, the starting point of disorder leading to tinnitus is still believed to be most commonly in the cochlea, although of course it can arise from disorders in the auditory nerve and in the central auditory pathways. The disordered cochlea leads to an alteration in the usual stream of nerve impulses going to the brain, and this may or may not be detected as if it was due to a sound. One might therefore expect the prevalence of tinnitus to be related to the amount of hearing disorder, the latter being most commonly indicated by degree of hearing impairment shown in the audiogram. Indeed, a high correlation between hearing threshold and tinnitus prevalence was found in the UK National Study of Hearing [1,2], see Figure 1.

It might be expected that one of the principal factors governing the severity of tinnitus would be its

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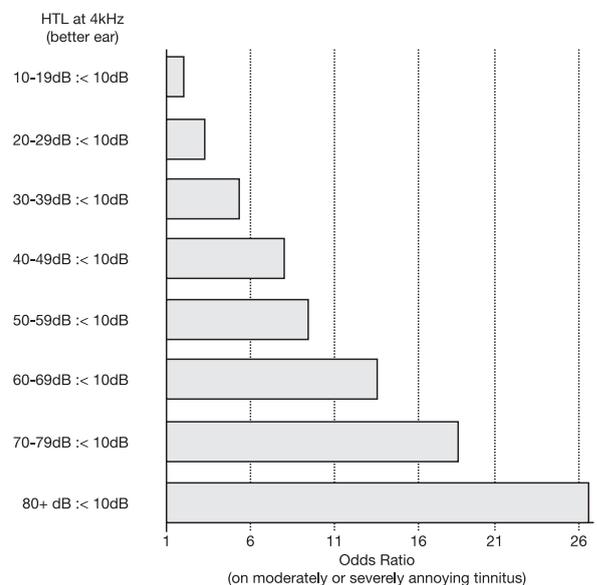


Figure 1 Prevalence of tinnitus: relation to hearing threshold level. (Data from UK National Study of Hearing, Phases 1, 2 and 3, tier B, n = 2522 adults) [1]

loudness. Indeed, the very word “severity” raises a question as to its meaning. Is it just the intensity of the sound? In that case loudness would be the primary measure of severity, perhaps together with some index of its acoustic unpleasantness, its “dys-

phony". Or is it solely the effect of the tinnitus on the individual? For most purposes, clinical and legal, what really matters is the degree to which the tinnitus causes distress of various kinds.

Nevertheless, the loudness of the tinnitus could be expected to be of some importance, particularly in the otocentric model where one might expect that the greater the abnormality of the neuronal signal the greater would be the distress caused. However, the more modern theories [e.g. 6] of tinnitus lay heavy emphasis on higher auditory processing and the way in which the person reacts to the tinnitus signal. Some degree of independence between tinnitus loudness and tinnitus distress might therefore be expected. On the other hand, it would usually be true that, in the case of an already distressed individual, if the loudness of the tinnitus increases over a few weeks or months then the amount of distress caused is likely to increase, and vice versa. Over a longer period though, that is quite often not the case. Epidemiological research [1] has shown a paradoxical association between loudness and annoyance: over the years studied, the most common change in tinnitus loudness was an increase whereas for annoyance it was a decrease. In some instances, these changes are found in the same individual [7].

One of the problems with looking at loudness in a quantitative way has been the distorting effects of loudness recruitment. A particularly telling example of this is to be found in the work of Tyler and Conrad-Armes [8]. In their subject number 10, the loudness matching was done at two different frequencies, one at the frequency of the tinnitus pitch and one at the frequency of the most normal threshold of hearing. The loudness matches in dB SL (sensation level) came out at 5.2 dB and 62.0 dB respectively. No wonder there are frequent difficulties in interpreting loudness match data!

This problem has been much reduced by the work of Matsuhira and colleagues in 1992 [4] who produced a nomogram for converting the tinnitus loudness sensation level, coupled with the threshold of hearing at that frequency, into an absolute loudness unit which they termed the Effective Loudness Level (ELL). In fact this corresponded to the loudness of an audiometric tone at that hearing level as heard by a normally-hearing person. At the 5th International Tinnitus Seminar, we reported on the effective loudness levels found in 103 patients at the Nottingham Tinnitus Clinic [4]. The median ELL was only 21 dB HL, ranging from 0 to 65 dB. Similar results were reported by Matsuhira and colleagues [5] from an otolaryngology clinic in Japan. In 525 patients their median value was 16 dB HL, ranging from 6 to 63 dB.

The interesting things about these absolute loudness data were the low median values, only 16 dB HL in otolaryngology clinic patients and 21 dB HL in a specialist tinnitus clinic, and that their maximum loudness after correction for threshold elevation and loudness recruitment effects was only in the region of 60–70 dB HL.

This naturally leads to the question as to why so

many of our patients with quite a soft tinnitus, with an ELL at or less than 21 dB HL, should have experienced so much distress from their tinnitus that they had been referred to a specialist tinnitus clinic? So the next stage in our study was to look at the relationship between those loudness measurements and the degree of distress caused. Luckily the data recorded on clinical patients was sufficient to permit this evaluation. Its results form the main subject of this paper.

Additionally, during preparation of this work, there came a legal question. This arose from a presumption by a particular lawyer that as the person claiming compensation had near-normal hearing his tinnitus could not be very loud. This led to further analysis, to look at the relationship between hearing threshold and tinnitus loudness.

Methods

The methods used are described in our paper in the previous International Tinnitus Seminar [4]. Briefly, we looked at data from 660 new patients seen at the Nottingham Tinnitus Clinic between February 1990 and October 1993. Strict exclusion criteria were applied, the main ones being those whose tinnitus at the time of test was not at its usual loudness, those with intermittent or variable tinnitus, those showing difficulties in carrying out the audiometric tinnitus tests, and those with an air-bone gap of 10 dB or more. 103 patients remained, for whom we had data on the hearing threshold level, tinnitus loudness match level and their overall assessment of the degree to which their tinnitus troubled them. The latter came from a questionnaire in which they had reported on the reduction in quality of their life due to tinnitus. The response options were none, very slight, slight, moderate, great, complete. From the combination of hearing threshold level and tinnitus loudness match data, we calculated the effective loudness levels (ELL) of the tinnitus according to Matsuhira *et al* [3].

Results

The principal result, covering the relationship between tinnitus loudness and tinnitus distress, is shown in Figure 2. There was in fact no statistical relationship between them. In particular, it should be noted how some patients with very low tinnitus loudness levels nevertheless reported moderate or great reduction in quality of their life due to their tinnitus. At the other end of the scale, some patients with tinnitus loudness at least 10 dB greater than the average value of around 20 dB HL reported only slight or very slight effects from the tinnitus. Thus, it would seem that an isolated loudness match measurement in an individual patient tells us very little if anything about how troublesome the tinnitus may be.

In looking at the relations between tinnitus distress and hearing threshold, four expressions of

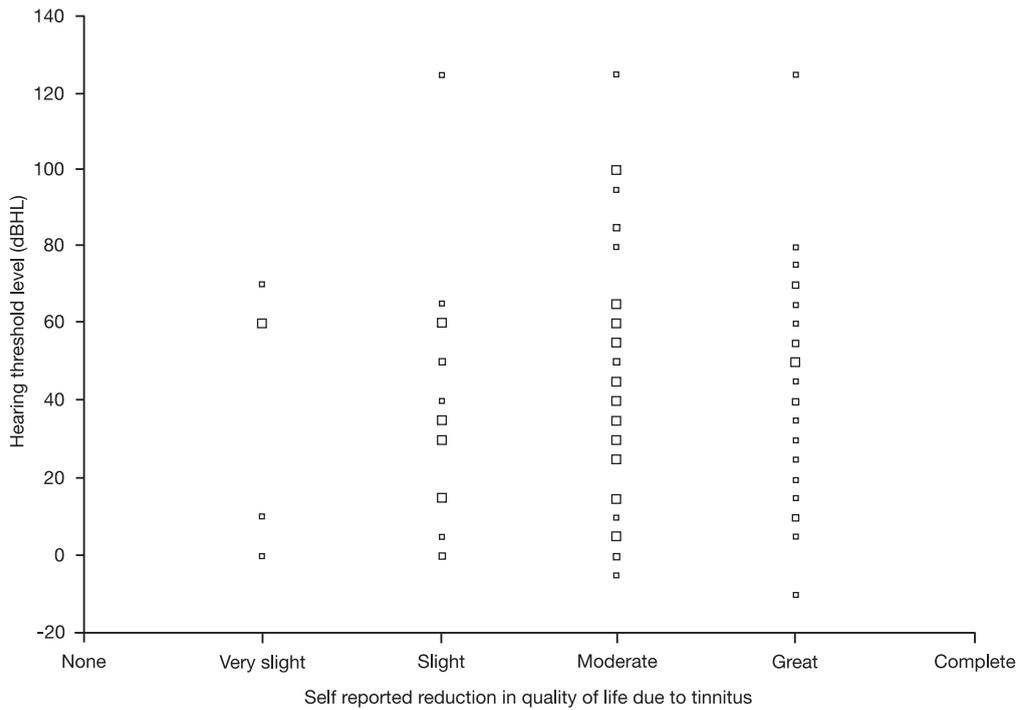


Figure 2 Relationship between tinnitus loudness and tinnitus distress (n = 103 patients).

threshold were considered. Two pairs of analyses used either the average impairment across 1, 2 and 3 kHz, the frequencies most commonly used in the UK for quantification of hearing loss for compensation purposes, or the threshold at 4 kHz. Each pair were studied either for the tinnitus-ear, taking the average between left and right ears where the tinnitus was not lateralised, or for the binaural weighted threshold. The weighting used was that com-

monly employed in UK for medicolegal purposes, weighting the better ear against the worse ear by a factor of 4 to 1. The Spearman correlation coefficients from these four analyses varied between 0.041 and 0.105, none of which were statistically significant. The case having the highest correlation, that concerning the thresholds averaged over 1, 2 and 3 kHz in the tinnitus ear, is shown in Figure 3. From the medicolegal viewpoint, it should be noted

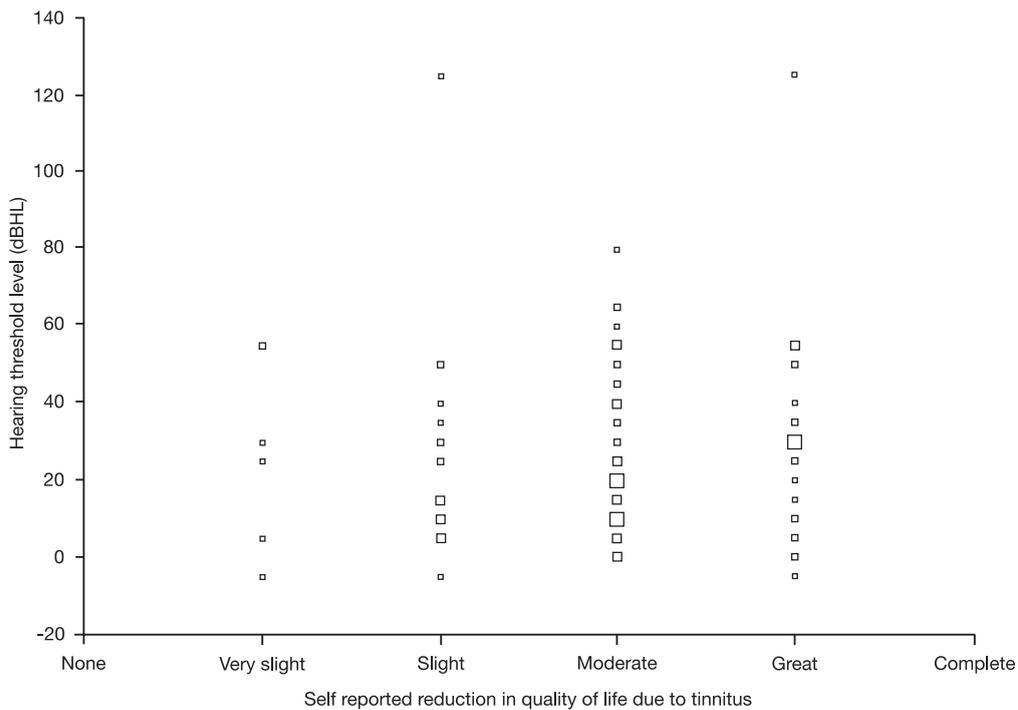


Figure 3 Relationship between hearing threshold and tinnitus distress (Tinnitus-ear thresholds averaged over 1, 2 and 3 kHz, n = 103 patients)

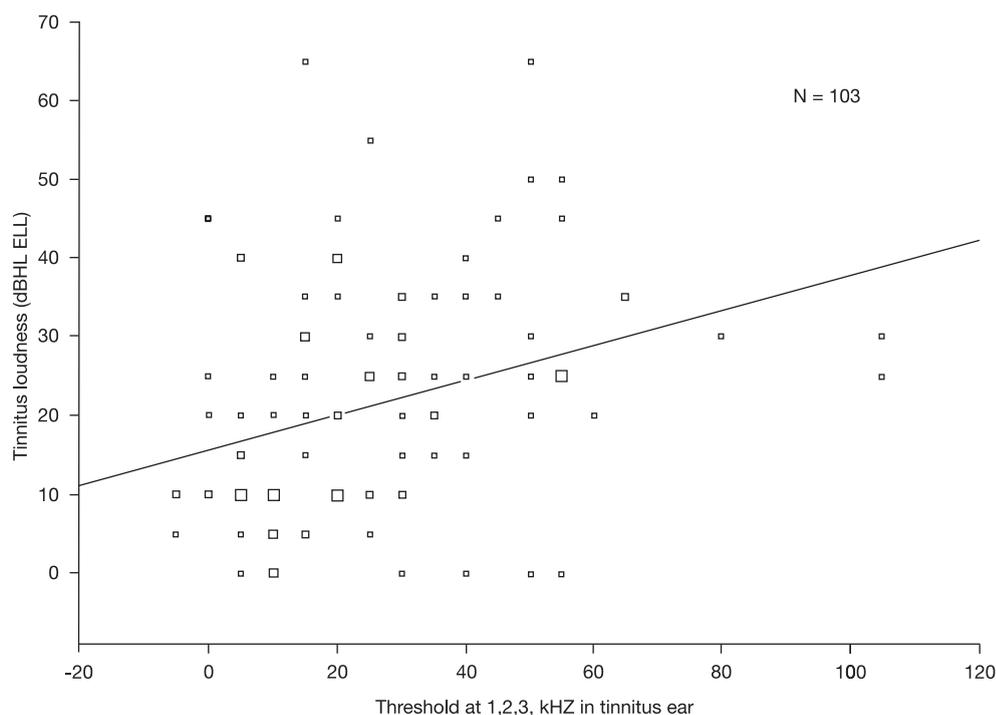


Figure 4 Relationship between hearing threshold and tinnitus loudness (Tinnitus-ear thresholds averaged over 1, 2 and 3 kHz, $n = 103$ patients) (Pearson $R = 0.332$, $P = 0.001$)

that a considerable number of those with moderate or great tinnitus distress had hearing threshold levels of 20 dB or less. Also, some of those with high hearing thresholds reported slight or very slight tinnitus. This is entirely in keeping with epidemiological data, where some people with severe hearing impairment have no tinnitus and others with wholly normal hearing do have tinnitus.

The only significant correlations we found in these studies were between each of the hearing threshold level indices studied and the tinnitus loudnesses. The correlation coefficients ranged from 0.286 to 0.395 (Spearman) or 0.269 to 0.332 (Pearson). Thus, although the correlation coefficients were significant, they were still quite small. The results in the analysis giving the highest correlation are shown in Figure 4.

Discussion and conclusion

The results of this study are interesting in two main ways. They provide evidence on the value, or perhaps lack of value, of audiological measurements in relation to tinnitus severity. They are also interesting in relation to modern theories of the mechanisms of generation of tinnitus itself and of tinnitus distress.

On the basis of this study, it appears that for assessment of severity, either for clinical purposes or for compensation assessment, matching tests of tinnitus loudness are virtually useless. For research, although loudness matches would not be satisfactory for matching of subjects in different treatment groups, serial measurements of tinnitus loudness might be of some use for relatively objective quantification of changes in loudness.

Measurements of hearing threshold likewise tell us very little about the degree of effect that the tinnitus is likely to have on a particular patient. On the other hand, in the UK National Study of Hearing, there was a weak correlation between self-reports of degrees of hearing difficulty and of annoyance caused by their tinnitus [1]. This was also true of hearing threshold measurements at high frequencies and degree of reported annoyance (A C Davis, personal communication, 1998). Indeed, one might well expect those who have greater difficulties in hearing external sounds to hear their own internal neurological sound, tinnitus, rather louder. This could be due to a mixture of over-attention to their hearing problem and of its attenuating effect on ambient sounds which otherwise would have had some masking effect on the tinnitus. One would also expect hearing difficulties and tinnitus to summate to some extent in terms of their effects on quality of life. In clinical terms, this of course reinforces the need to do what we can to rehabilitate the hearing and hopefully this will then reflect positively on the patient's tinnitus.

For legal purposes though, we cannot deduce anything useful about the severity of the tinnitus from measurements of the person's hearing threshold and we should resist any suggestion that the tinnitus cannot be severe because the person's hearing is good. With such evidence, particularly that shown in Figure 2, it seems that the only useful index of tinnitus severity is to take a detailed history of the effects of the tinnitus on the person, his family and his work, and perhaps administer one of the properly validated assessment questionnaires available,

Coming now to theoretical considerations. The

correlation between hearing threshold and prevalence of tinnitus (in adults) is an obvious one, and relates to the probability that most cases of tinnitus originate with some disorder in the cochlea. The greater the cochlear disorder, the greater the likelihood of tinnitus occurring. Likewise, the greater the disorder, probably the greater the magnitude of the abnormality of neuronal signal going to the central auditory centres, and the greater the loudness of the tinnitus, both in itself and because of the tinnitus-enhancing effects of the hearing impairment.

But the switch of emphasis from the ear to the brain, optimised in Jastreboff's neurophysiological model of tinnitus [6], would lead us to expect a considerable degree of independence between measurements of hearing and tinnitus on the one hand and on the other the degree of disturbance caused by the tinnitus, the latter depending heavily on cognitive psychological evaluation of the tinnitus and on neurological links with the limbic and autonomic nervous systems. The lack of correlation found here between the measurements of tinnitus and the degree of distress reported by these patients seems to fit in very well with the concepts proposed in the Jastreboff model.

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The Zwicker tone (ZT) as a model of phantom auditory perception

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The Zwicker tone (ZT) is a phantom auditory sensation which follows the presentation of a wide band noise containing a spectral notch. Apart from the fact that it is temporary, the ZT sensation, which resembles that elicited by a faint sinusoidal tone with a frequency akin to the center of the notch, is comparable in many respects to tonal tinnitus. The ZT has the advantage over tinnitus that its characteristics (in particular, its frequency) can be controlled to a large extent, and that it can be studied in normal-hearing subjects. Therefore, the ZT might provide a convenient human model for the investigation of the mechanisms underlying the generation of phantom auditory sensations. In an earlier study, the ZT elicited by a notched noise was shown to be accompanied by enhanced hearing sensitivity around the center frequency of the notch. In the present study, we hypothesized that this auditory enhancement effect involved a lateral inhibition mechanism which should also result in threshold deterioration effects around the borders of the spectral notch. This prediction was confirmed by the results of a first experiment. The results of a second experiment revealed that when the notched-noise inducer was presented diotically, a significant enhancement in hearing sensitivity was observed only in one ear, and that this ear corresponded to that in which a ZT was perceived. These results agree with the notion that the ZT and the threshold enhancement phenomena are related. Overall, the results of the present study constitute a further step toward the development of a model of phantom auditory perception in humans and they further support the potential interest of this model in understanding the underlying mechanisms of phantom auditory sensations.

Introduction

The term illusion refers to the idea that perception is not always a faithful reflect of reality. Perceptual illusions constitute an invaluable tool for studying the mechanisms by which sensory information is processed by the human brain. In the auditory modality, an example of pathological illusion is known as tinnitus. Tinnitus is generally defined as an auditory sensation in the absence of corresponding sound in the environment.

The Zwicker Tone (ZT) is a negative auditory afterimage which is evoked when a notched-noise (NN) presented during several seconds is stopped. Zwicker [1] was the first author to discover this effect in hearing. He studied the properties of the perception itself and the characteristics of the inducer required to elicit it. The main results that he obtained can be summarized as follows: Firstly, the subjective perception is similar to a sinusoidal tone, with a pitch within the suppressed frequency range of the NN. Secondly, the pitch of the ZT increases

with the level of the inducer. Thirdly, the ZT can be obtained with NN containing suppressed bands one half-octave wide for center frequencies between 700 Hz and 6 kHz. Fourthly, the duration of the ZT increases with the duration of the inducer. Finally, a continuous ZT sensation can be induced by presenting 100-msec notched-noise bursts at a repetition rate of about 5 Hz.

Surprisingly, apart from this initial study by Zwicker, only few investigations have been devoted to the ZT. Following Carlyon [2] who showed that signal detection in noise could be enhanced by the presentation of a notched noise, Wiegrebe *et al.* [3] demonstrated a decrease in the absolute threshold of a tone pip following the presentation of a 1-sec noise burst which contained an half-octave-wide notch, and which was known to induce a Zwicker tone. This auditory enhancement effect was found to be largest around the center frequency of the notch, which corresponded to the perceived frequency of the ZT.

More recently, insights into the neural substrate of the phenomenon was provided by the results of Hoke *et al.*, who carried out magnetoencephalographic (MEG) recordings during a ZT sensation in normal-hearing subjects [4,5]. The results indicated that the cortical region activated during the

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ZT sensation was similar to that activated by a tone of the same frequency. The authors concluded that the mechanisms underlying the ZT were similar to those involved in the perception of an external tone. In other words, the ZT is likely to result from the brain mistaking an aberrant neural signal for a real sound of the external world.

The general hypothesis subtending the present work is that insights into the mechanisms underlying tinnitus can be gained by studying the state of the auditory system in situations in which a ZT is being perceived by the listener. From that point of view, the ZT provides an ideal experimental tool since: (a) it can be elicited in normal-hearing subjects, (b) it is entirely reversible, and (c) its characteristics (in particular, its frequency) can be controlled. Furthermore, in contrast to tinnitus, which is generally permanent, with the ZT, control conditions in the same subject are available.

More specifically, two hypothesis were tested in the present study: The first hypothesis was that the changes in absolute sensitivity which follow the presentation of a notch-noise and accompany the perception of a ZT are underlain by a lateral inhibition process. This hypothesis predicts that the threshold-enhancement effect observed at frequencies akin to the center of the notch should be accompanied by a threshold-deterioration effect at frequencies just outside this notch. In order to test this hypothesis, the absolute thresholds of probe tones having different frequencies, within and outside the spectral notch were measured following either a notched noise or white noise.

The second hypothesis that was tested in this study was that of a relationship between the ZT sensation and the threshold enhancement effect. In order to test this hypothesis, advantage was taken of the fact that the diotic presentation of a notch noise generally results in a monaural ZT sensation. Consequently, we tested whether the threshold enhancement effect was specific to the ear in which the ZT was perceived.

Experiment 1: Measure of absolute threshold following the presentation of notched noise.

Methods

Subjects

Nine normal-hearing subjects aged between 20 and 30 years took part in this experiment. Due to the relatively long duration of the tests, not all probe frequencies could be tested in all the subjects (Table 1).

Stimuli

The stimuli used in this study consisted of bursts of broadband or band-rejected noise, and of tone bursts. The noise bursts were 1-sec long and their overall level was set to 40 dB SPL. The broadband noise contained frequency components between 0 and 15 kHz. The notched noise was generated by cancelling all spectral components between 3400 and 4800 Hz (i.e. roughly $\frac{1}{2}$ octave around 4 kHz). The signals consisted of a sequence of four tone bursts, 130-ms long each (including 20 ms cosine ramps), and separated by 130-ms long silent gaps. All stimuli were generated digitally using a 16-bit quantization range and a 40 kHz sampling rate. The noise bursts were generated by digital convolution of a burst of gaussian noise with the impulse response of a rectangular filter computed by inverse FFT. The stimuli were presented monaurally to the subjects, the tested ear being randomized across subjects.

Procedure

Absolute thresholds were measured using a two-interval, two-alternative, forced-choice (2I-2AFC) procedure. A two-down, one-up tracking rule estimated the 70.7% correct point on the psychometric function. Each interval contained a burst of notched noise or white noise. In one interval, chosen pseudo-randomly on each trial, the burst was immediately followed by a sequence of probe tones (as described above). The subjects' task was to indicate if the probe tones were present in the first or in

| Subject | Test frequencies (kHz) | | | | | | | | | |
|---------|------------------------|---|-----|-----|---|-----|---|-----|-----|--|
| | 2,8 | 3 | 3,2 | 3,8 | 4 | 4,4 | 5 | 5,2 | 5,4 | |
| 1 | 2,8 | 3 | 3,2 | 3,8 | 4 | 4,4 | 5 | 5,2 | 5,4 | |
| 2 | - | 3 | - | - | 4 | - | - | - | - | |
| 3 | - | 3 | - | - | 4 | - | - | - | - | |
| 4 | - | 3 | - | - | 4 | - | - | 5,2 | - | |
| 5 | - | 3 | 3,2 | - | 4 | - | - | 5,2 | - | |
| 6 | 2,8 | 3 | 3,2 | 3,8 | - | 4,4 | 5 | 5,2 | 5,4 | |
| 7 | 2,8 | - | 3,2 | 3,8 | 4 | 4,4 | 5 | 5,2 | 5,4 | |
| 8 | 2,8 | 3 | 3,2 | 3,8 | 4 | 4,4 | 5 | 5,2 | 5,4 | |
| 9 | 2,8 | 3 | 3,2 | 3,8 | - | 4,4 | 5 | 5,2 | 5,4 | |

Table 1 Probe frequencies tested in the 9 subjects of experiment

the second interval. The procedure stopped after 12 reversals in the signal level. Threshold was computed as the average signal level over the last 8 reversals. The initial step size, 3 dB, was reduced to 1 dB after the fourth reversal. At least 3 thresholds estimates were obtained at each probe frequency tested.

Apparatus

Stimuli were played out, low-pass filtered, attenuated, mixed and sent to Sennheiser HD465 headphones using Tucker Davis Technologies modules (DA2, AAF, PA4, SM3, and HB6).

Results

Figures 1 and 2 represent the differences in absolute thresholds measured following the broadband noise and the notched noise. Negative differences indicate an enhancement in absolute sensitivity following notched noise, as compared to broadband noise. The statistical significance of the results was tested

using a one-way repeated-measures ANOVA. For the analysis, the data obtained at the different frequencies were grouped into three bands: one band for frequencies falling within the notch (i.e. 3800, 4000, and 4400 Hz), one band for frequencies below the notch (i.e. 2800, 3000, and 3200 Hz), and one band for frequencies above it (i.e. 5000, 5200, and 5400 Hz). One-way ANOVA showed a significant frequency effect ($p < 0.05$). The results of Fisher's post-hoc tests revealed the existence of a significant auditory enhancement effect within the spectral gap ($p < 0.05$). They also revealed the opposite effect for frequencies located near the low- and high- cutoff-frequencies of the gap ($p < 0.05$).

Experiment 2: Effect of bilateral notched noise on absolute threshold

Methods

Subjects

Five normal-hearing subjects aged between 20 and 30 years took part in this experiment.

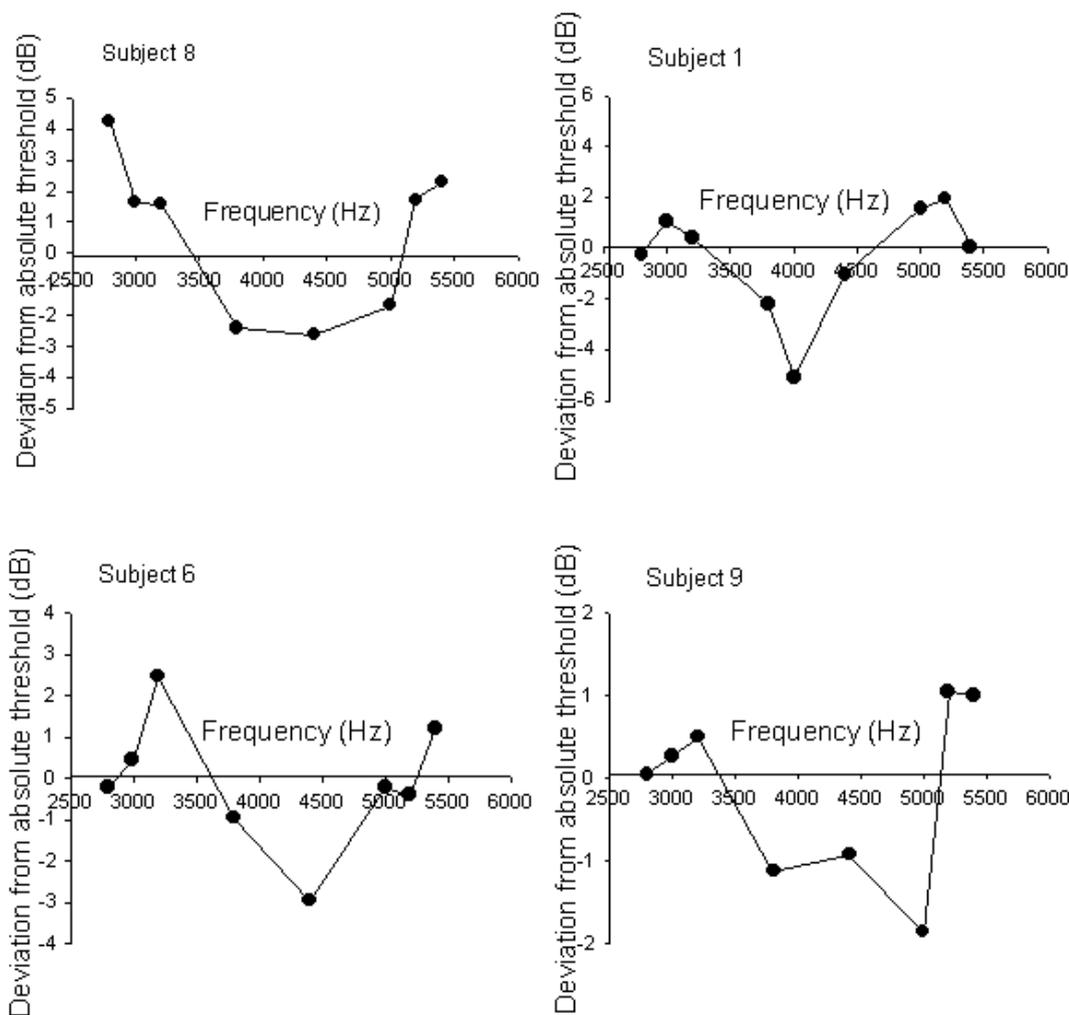


Figure 1 Differences in absolute thresholds (\pm SEM) between probe tones following a broadband noise or a notched noise in four subjects.

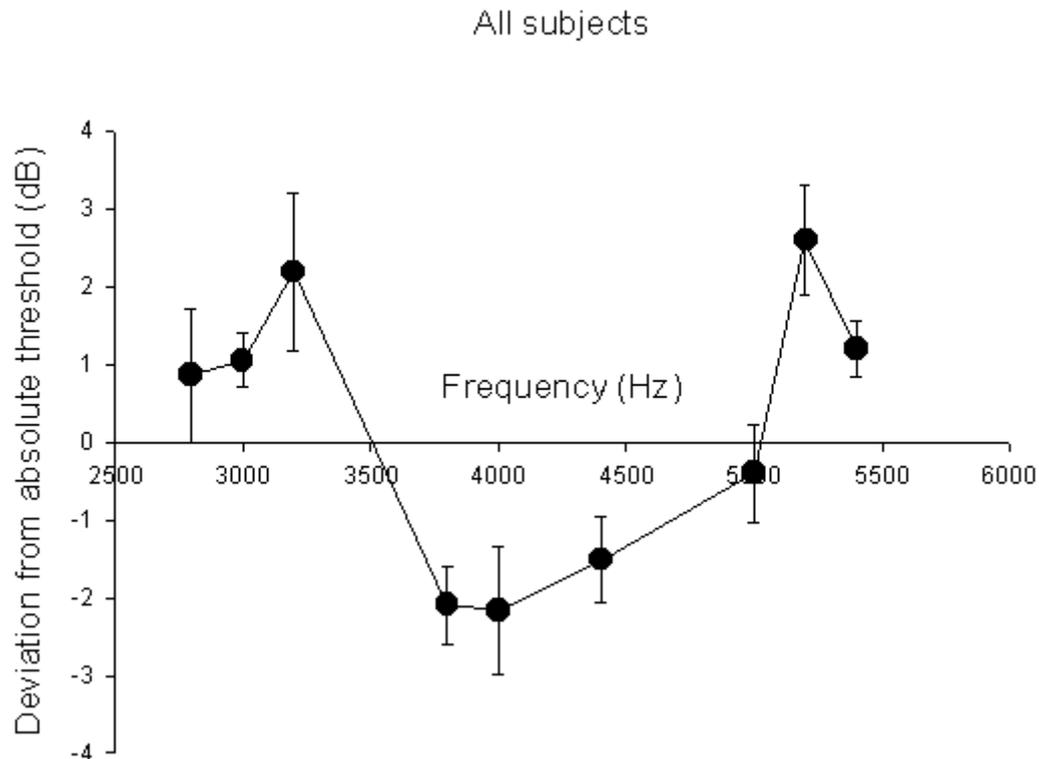


Figure 2 Difference in absolute threshold (\pm SEM) between probe tones following a broadband noise or a notched noise averaged over all the subjects.

Material and procedure

The same material, procedure, and stimuli as those used in experiment 1 were used in this second experiment, except for the fact that the noise bursts were presented diotically, and that absolute thresholds were measured successively in the two ears. Furthermore, all subjects were asked to report in which ear the ZT sensation elicited by the diotic presentation of the notched noise was heard.

Results

The results of the questionnaire in which the subjects had to indicate whether the ZT was heard in the right, the left, or both ears revealed that the ZT elicited by the presentation of diotic notched-noise was systematically heard monaurally. Although the ear in which the ZT was heard varied across subjects, it was always the same on different presentations of the diotic noise in a given subject.

The results of this second experiment further revealed that, following the presentation of a diotic inducer, a significant threshold enhancement effect comparable to that observed in the first experiment occurred in the ear in which the ZT was heard ($p < 0.05$), but not in the opposite ear ($p > 0.05$) (Figure 3).

Discussion

The first main outcome of the present study consists of the fact that, besides threshold enhancement effects at probe frequencies falling within the notch of the preceding inducer, significant threshold deterioration effects occurred for probe frequencies below and above the low and high cutoff frequencies of the notch. The second main outcome corresponds to the fact that when the inducer was presented diotically, the ZT sensation was lateralized – i.e. perceived in one ear rather than in both ears or in the middle of the head – and the threshold enhancement effect was systematically larger on the perceived side of the ZT than in the opposite ear.

The neurophysiological mechanisms underlying the ZT are unclear. Wiegrefe *et al.* [3] investigated the possible role of cochlear mechanisms in the generation of the ZT. They found that although the perceived intensity of a spontaneous otoacoustic emission (SOAE) was increased after the presentation of a noise having a notch centered on the SOAE frequency, the physical intensity of the SOAE remained unchanged. Furthermore, neither the perception of the ZT nor the threshold enhancement effect were significantly influenced by a simultaneous, low-frequency tone pip introduced to bias the cochlear mechanics. The authors concluded that the ZT and the auditory enhancement phenomena were very unlikely to have their origin at the level of the cochlea. Physiological recordings by Palmer *et al.* [6] further suggest that the auditory enhancement effect is not present at the level of the

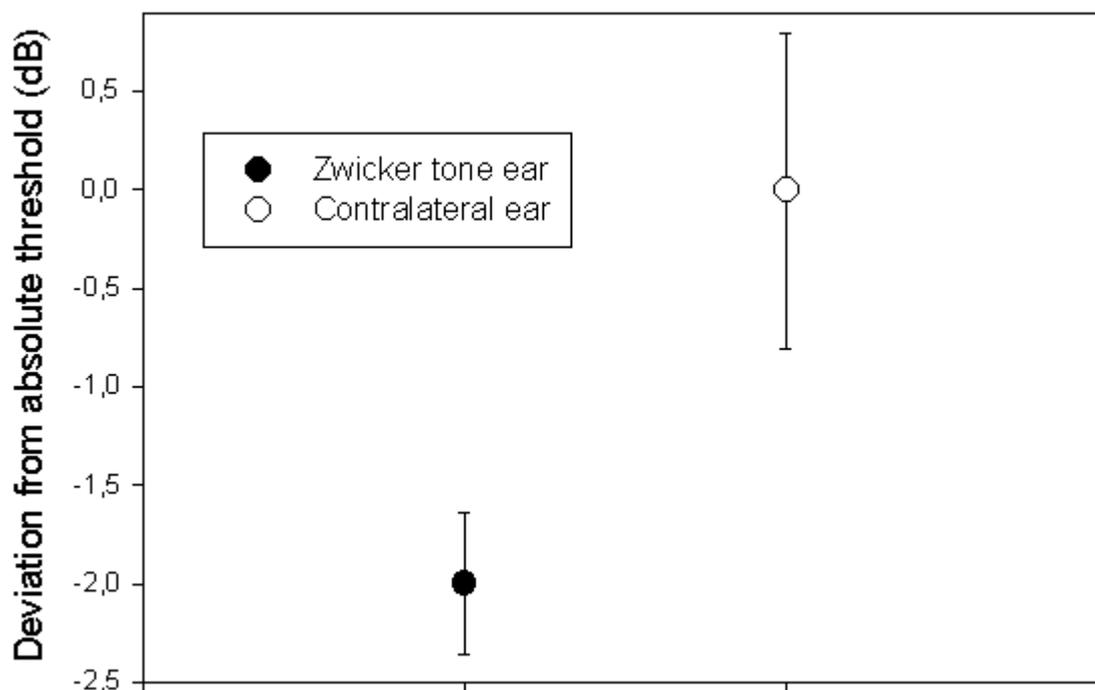


Figure 3 Difference in absolute threshold (SEM) between probe tones following the dichotic presentation of broadband or notched noise.

auditory nerve. Consequently, it appears likely that the phenomena under study originate in central stages of the auditory system.

An explanatory mechanism for the enhancement effect at the level of the cochlear nucleus has been tentatively put forward by Wiegrebe *et al* based on existing physiological data. Their reasoning is based on the notion that the selective inhibition of neurons in the ventral cochlear nucleus (VCN) by units from the dorsal cochlear nucleus (DCN) results in a “whitening” of the spectral representation conveyed toward higher auditory centers by the cochlear nucleus [7,8]. This spectral-contrast reduction mechanism, which proceeds by inhibiting less units that respond to frequencies in the region of the notch than units with center frequencies outside the notch, might be the origin of the psychophysical enhancement effect.

In order to account for the finding, in the present study, of threshold deterioration effects outside the notch, one would further have to assume that units with center frequencies akin to the border of a spectral notch behave differently than units having center frequencies within or far away from the notch. From a more general point of view, the pattern of results evidenced in the present study, with enhancement in the notch, deterioration just outside the notch, and no effect at more distant frequencies, is reminiscent of the mexican-hat shape which is characteristic of lateral inhibition processes. Such neural lateral-inhibition mechanisms are known to take place at the level of the cochlear nucleus.

Interestingly, some authors have suggested an involvement of the DCN in the mechanisms under-

lying tinnitus. Eggermont [9] proposed that the DCN and the external lemniscal pathways could be preponderant in the generation of salicylate-induced tinnitus. Kaltenbach [10] found enhanced spontaneous activity in the DCN after auditory trauma and suggested that this enhanced activity could be a direct physiological correlate of tinnitus. It is noteworthy that an involvement of the DCN has been proposed to account both for tinnitus and the ZT.

The results of Hoke *et al.* reveal that the ZT is represented by locally increased neural activity at the cortical level. This finding can be paralleled with the hypothesis that tinnitus results from increased spontaneous activity in the auditory system [11], as well as with the notion that fibers with low thresholds exhibit larger amounts of spontaneous activity. If indeed phantom auditory sensations like tinnitus or the ZT correspond to local increases in spontaneous neural activity, and these increases are concomitant to a reduction in the units threshold, then the enhancement effect, the ZT, and tinnitus may share a common underlying neurophysiological basis.

An argument for the notion of an underlying link between the ZT and threshold enhancement effects is provided by the present finding that when the two ears were stimulated with the same burst of notch noise, a threshold enhancement effect was observed in the ear in which the ZT was perceived, but not in the opposite ear. This finding is surprising since it was originally expected that the diotic presentation of notch noise would lead to a binaural, rather than a monaural ZT sensation, and that the auditory enhancement effect would be obtained in both ears.

In an earlier study [12], it was found that the presentation of diotic notched noise induced a ZT sensation in the middle of the head. This apparent discrepancy between the present and earlier results may be explained by intersubject variability, or by methodological differences. Further study on this point is certainly in order.

In conclusion, the present results provide further insight into the nature of the mechanisms underlying changes in absolute sensitivity observed concomitantly to the generation of a tonal auditory sensation; specifically, they suggest an involvement of lateral inhibition processes in the phenomenon. The results also indicate the existence of a relationship between the auditory enhancement effect, and the ZT sensation by showing a correspondence between the ear in which the ZT is perceived and the ear in which the enhancement effect is observed in diotic stimulation conditions. Following these encouraging results which confirm the potential interest of the ZT and of changes in absolute hearing sensitivity for the investigation of the underlying mechanisms of phantom auditory sensations, future research work will be directed at testing for relationships between the characteristics of the ZT and those of tinnitus. One of the main questions that will need to be addressed in this perspective concerns the main differences between a temporary auditory illusion like the ZT and a permanent phantom auditory sensation, like tinnitus.

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Tinnitus loudness and pitch matching: Various techniques with a computer- automated system

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As described in a companion paper, this laboratory has developed a psychoacoustical testing system to perform computer-automated tinnitus loudness and pitch matching. Subjects respond to testing using a touch-sensitive video screen. Loudness matching data have previously been reported, and reliability was seen to be good both within and between sessions (Pearson $r = 0.889$ and $p = 0.0001$ for repeated loudness matches at 13 frequencies). Basic results of that study are presented here along with two studies using the automated system to evaluate the reliability of tinnitus pitch matches using four different methods.

Introduction

During most tinnitus evaluations an attempt is made to identify the level of a tone that matches tinnitus loudness, and the frequency of a tone that closely matches the predominant tinnitus pitch. However, methods for loudness and pitch matching have not been standardized. More basically, clinical protocols for tinnitus matching have not been documented for test-retest reliability of the measurements. Studies providing data on repeated loudness and/or pitch matches have shown discrepant results, with many indicating poor reliability (see [1] for a review).

The present report briefly describes results of three studies from which repeated tinnitus matches were obtained. Study 1 was conducted to document test-retest reliability of tinnitus loudness matches at a series of 13 frequencies. The second study evaluated two variations of an automated technique that were used in an attempt to determine which method provided the greatest test-retest reliability of pitch matches. In Study 3, results of two methods for automated pitch matching were compared to results obtained using a conventional manual procedure for tinnitus pitch matching.

Methods

Subjects. Twenty subjects participated in Study 1, and 20 subjects completed Study 2. Study 1 included two females and 18 males with a mean age of 58.0 years. Study 2 included three females and 17 males (mean age 60.1 years). Forty-two subjects completed Study 3, including 8 females and 34 males (mean age 59.9 years). All subjects were selected on the basis of having tonal, stable tinnitus in order to minimize any variability in the tinnitus that might confound interpretation of the reliability analyses.

Equipment. The computerized system used for these studies has been previously described [2]. It is also described in a report found elsewhere in these Proceedings ("Fully automated system for tinnitus loudness and pitch matching"). Briefly, the system consisted of two computers that were physically and programmatically linked. The "main" computer sat in the control room and ran the overall program. The "subject" computer ran a touch-sensitive video screen that provided instructions for subject responding, and allowed subject responses directly on the screen.

Slightly different versions of the system were used for the different studies. For Studies 1 and 2, the three major hardware components of the tinnitus testing system included: (1) the main computer (Dell Dimension 166 MHz Pentium CPU) and signal generator; (2) a custom-built signal conditioning module for signal mixing, attenuation, and headphone buffering (Oregon Hearing Research Center, Portland, OR); and (3) the subject computer (Compaq Concerto 4/25).

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For Study 3, hardware and software modifications were made to the subject computer system. In summary, the pen-enabled-touch Concerto computer was replaced by a human finger-enabled-touch LCD monitor with a desktop computer controller. Several text and layout modifications were made to the subject message and response dialog forms for resizing and general clarity reasons. A subject-guided pitch match test was added as another test protocol available for use in automated tinnitus testing. Support for "Manual" test set execution and stimulus level control with automated data logging was added to the program.

Calibration for all studies was done by a stand-alone Instrument Manager application that was developed to perform automated calibration and store the data in an instrumentation database. This instrumentation database was run-time accessed by the testing program to provide calibrated stimulus levels.

General procedure for automated tinnitus matching. Generally, testing started with the automated measurement of hearing threshold at a test frequency, followed by a loudness match at the same frequency. A threshold and loudness match were then obtained at the next higher frequency. For Study 1, this paradigm was repeated in order of ascending frequencies. For the pitch matching studies, the first two loudness-matched tones were presented, one following the other, and the subject chose which of the two tones sounded closest in pitch to his/her tinnitus (i.e., two-alternative forced choice, or 2AFC). Dependent upon the frequency choice, the computer then increased or decreased the frequency and obtained a threshold and loudness match at the next test frequency. These last two loudness-matched tones were then presented, and the subject again chose which of the two tones sounded closer in pitch to his/her tinnitus. In this fashion, the computer progressively stepped up or down in frequency until the tinnitus pitch was bracketed to within a specified range. The computer then stepped up in 1/3 octave steps and, choosing the closest pitch with the 2AFC procedure, the subject chose a final tinnitus pitch match. Octave confusion testing was then performed.

Study 1: Repeated tinnitus loudness matches

There were two objectives for Study 1: (1) document test-retest reliability of tinnitus loudness matches at a series of 13 frequencies; and (2) evaluate if there was any decrease in response reliability when *randomization* was applied to the start level of loudness matching tones and to the step sizes for increasing the level of the tones. All procedures were conducted over two testing sessions, separated by 1–14 days. Two experimental loudness match protocols, Fixed and Random, were completed during each session. Test frequencies for hearing thresholds and tinnitus loudness matches were in the range 1–16 kHz, and separated by 1/3 octaves.

Study 2: Two automated procedures for tinnitus pitch matching

"Octave" Procedure. The computer first bracketed the pitch match to within an octave, starting at 1 kHz. Test frequencies usually went up from 1 kHz (because most patients have tinnitus above 1 kHz), until the octave range was bracketed, at which time the computer found a pitch match with 1/3-octave resolution.

"Binary" Procedure. The computer bracketed the tinnitus pitch to within an octave, starting at 4 kHz. The test frequencies increased or decreased from 4 kHz, depending on the choice the subject made for the first pitch match.

Study 2: One manual and two automated procedures

"Manual" Procedure. The tinnitus pitch matching procedure that has been documented for clinical tinnitus evaluation at the Oregon Tinnitus Clinic was used for this portion of the study. The automated system was configured to facilitate manual evaluation of hearing thresholds, tinnitus loudness matches and tinnitus pitch matches. The initial frequency was 1000 Hz, and frequencies were stepped up in 1000 Hz increments. A threshold and loudness match were obtained at each frequency, and the 2AFC procedure was used for subjects to make pitch choices. When the subject chose a final pitch match, octave confusion testing ensued.

"Binary" Procedure. This procedure was conducted in an identical fashion as described above for Study 2.

"Subject-Guided" Procedure. Following the Binary Procedure, loudness matches were obtained at all remaining 1/3 octave frequencies, from 0.5 to 16 kHz. The computer then selected one of these frequencies at random and presented it at the loudness-matched level. The subject directed the computer to make the tone "higher" or "lower" in frequency until a tone was presented that was selected as a pitch match. This procedure was repeated five times during each of two sessions.

Results

Study 1

Across-subjects means of the loudness matches, expressed in dB SPL are shown in Figure 1. Repeated measures ANOVAs were done for the four means at each frequency. Because of the large number of ANOVAs that were run, the alpha level was reduced to 0.01. The only significant difference was at 2 kHz ($p = 0.0068$).

The above analysis showed that the group of subjects as a whole provided reliable loudness matches between methods and between sessions. However, it did not address the *within-subjects* reliability of responses. Pearson 'r's were therefore calculated for all combinations of repeated loudness matches, both within and between sessions. Pearson 'r's for all

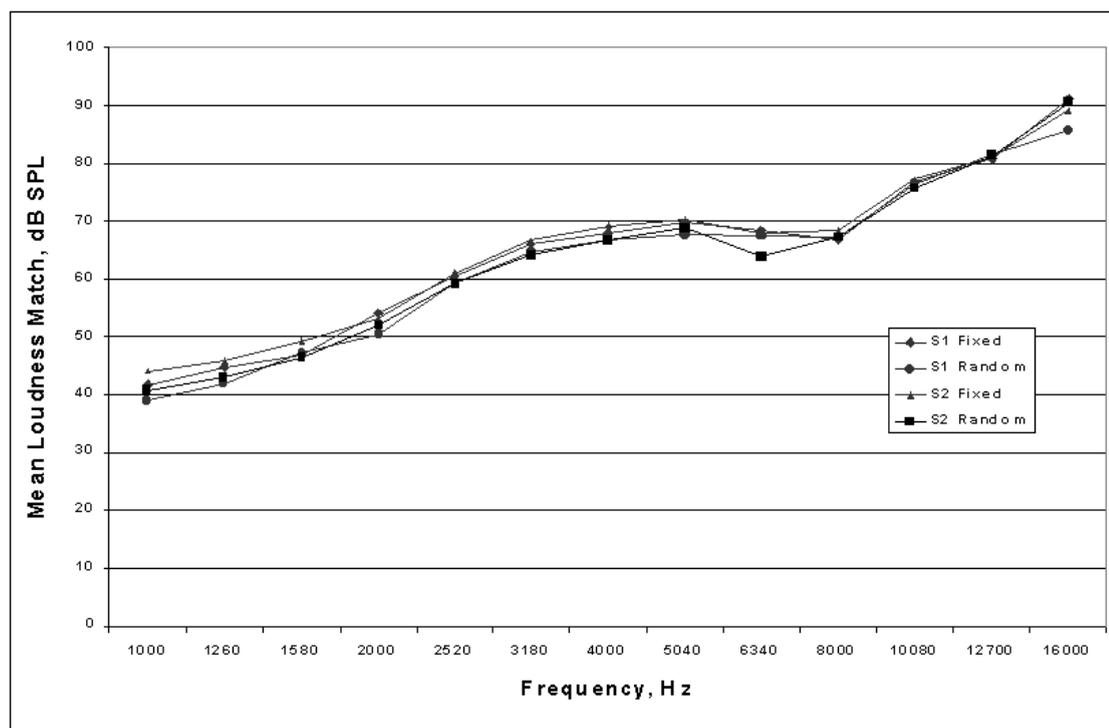


Figure 1 Mean loudness matches expressed in dB SPL. S = Session

loudness matches in dB SPL were greater than .889 and significant at $p < 0.0001$ (indicating that the measures varied together systematically). It was also found that there were no significant differences between Fixed and Random methods [2].

Study 2

Subjects were tested with both the Octave and Binary pitch match procedures over two sessions. There were thus two final pitch matches obtained with each procedure. Figure 2 shows a frequency distribution for all of the pitch matches over both sessions. It can be seen that in general the majority of pitch matches were in the upper half of the frequency range, with more scattered results in the lower half.

Figure 3 shows the actual pitch matches made by each subject, with vertical lines connecting the session 1 and session 2 responses (data shown only for Binary method – Octave method showed similar results). Subjects are ordered left to right on the abscissa from least variability between responses to most variability. It should be noted that the actual test frequencies in Hz were converted to their position in ascending order so that differences between frequencies would be spaced logarithmically – roughly equivalent to their relative spacing on the basilar membrane. Figure 3 reveals the large differences in reliability between subjects. It also shows that the most reliable subjects made pitch matches consistently in the upper half of the frequency range. Lower frequency responses occurred only for the least reliable subjects.

The across-subjects means of the pitch matches

were calculated for each method and each session. To evaluate if there were significant differences between the mean pitch matches, paired t -tests were calculated. The t -tests revealed that the between-session means of the Binary procedure did not differ significantly ($p = 0.2952$), but the means of the Octave procedure did ($p = 0.0198$). Thus, for the group, the mean pitch matches between Session 1 and Session 2 were significantly different only for the Octave procedure.

To evaluate more closely the *within-subjects* reliability of responses, differences were calculated between the Session 1 and Session 2 pitch matches for each procedure. For the Binary procedure, the Session 2 pitch match was subtracted from the Session 1 pitch match, and the mean of these differences was -742 Hz. When the same calculations were made for the Octave procedure, the mean of the differences was -2394 Hz. Thus, for both procedures, there was a trend for pitch matches to be higher in frequency during the second session, and the difference was much greater for the Octave procedure. These differences between sessions were fairly random between subjects, however, thus the trend was not significant.

Following the calculations of the mean differences between sessions, the absolute values of these differences were calculated. The means of the absolute values of the differences were 2246 Hz for the Binary procedure, and 3247 Hz for the Octave procedure. Thus, the magnitude of the differences was on average larger for the Octave procedure, but this difference between means was not significant (paired t -test, $p = 0.3282$).

Finally, Pearson product-moment correlation

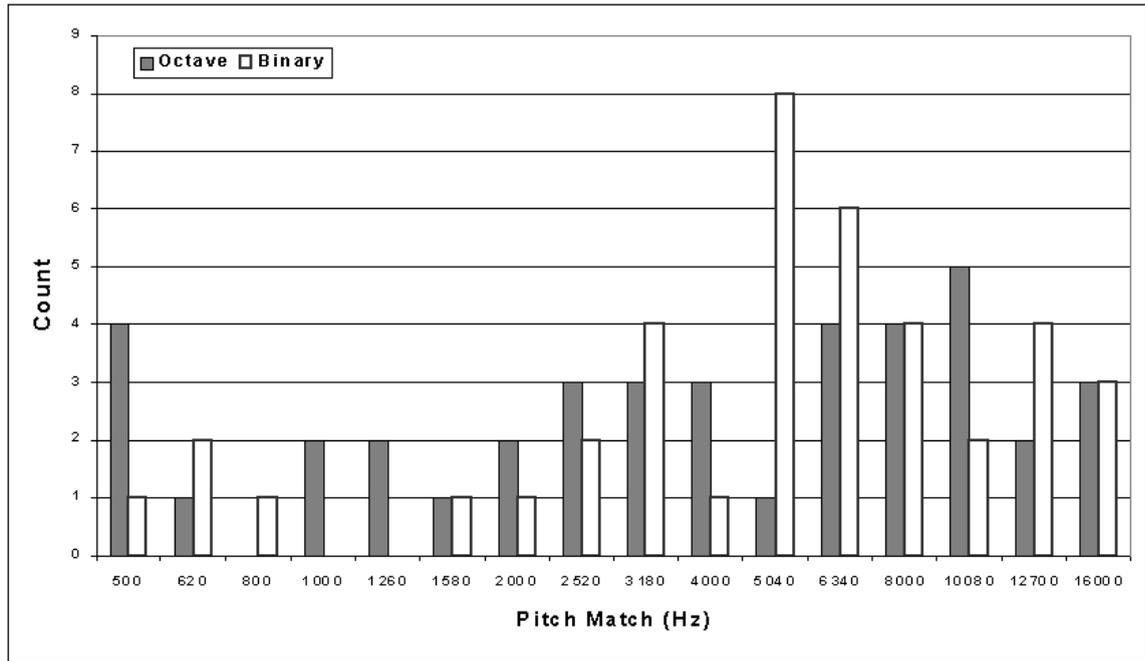


Figure 2 Frequency histogram for both methods, showing the number of matches for each test frequency.

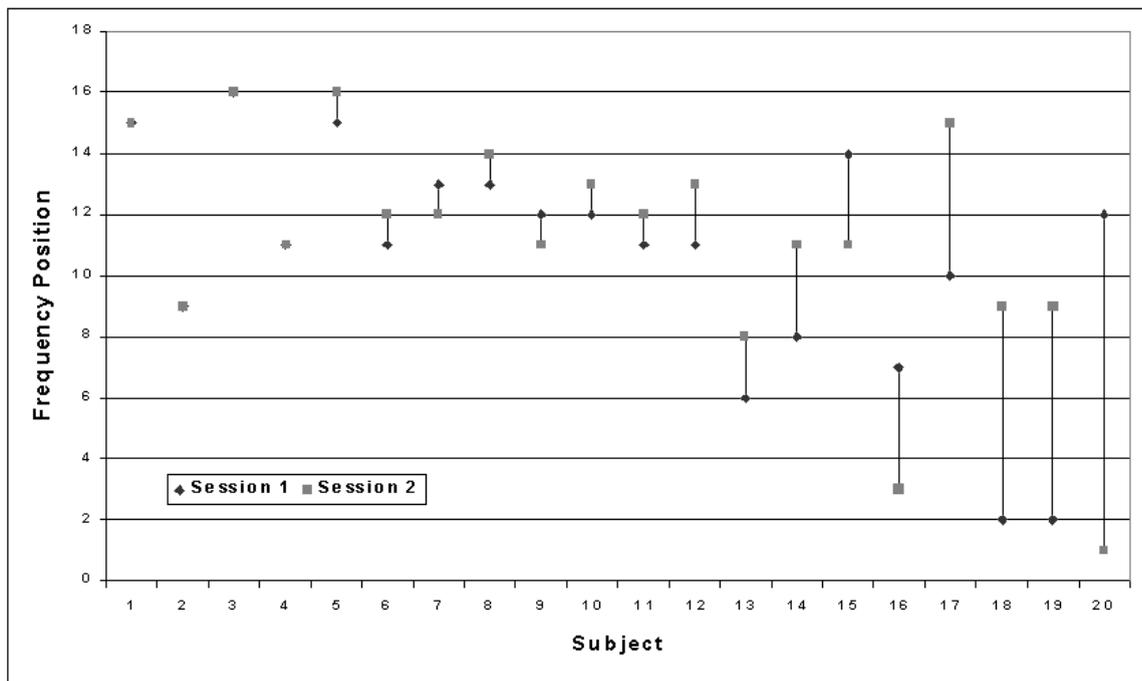


Figure 3 Scattergram showing pitch matches made by each subject, with vertical lines connecting pitch matches between sessions. (Single points indicate responses for both sessions were identical.)

coefficients were calculated between the Session 1 and Session 2 pitch matches for each procedure. For the Binary procedure, the Pearson r was 0.757 ($p < 0.0001$), and for the Octave procedure, the Pearson r was 0.589 ($p = 0.0053$).

Each of the above analyses generally supported the Binary procedure as providing more reliable

between-session tinnitus pitch matches than the Octave procedure. For this reason, the Binary procedure was used in the following pitch match study, to determine how it would compare to pitch match results using a manual procedure, and to results using a conceptually different automated pitch match procedure.

Study 3

Forty-two subjects were evaluated over two sessions using the Binary and Subject-Guided automated pitch match methods, as well as the Manual pitch match method. The frequency distributions of the pitch matches for each method were similar to that shown in Figure 2, and the variability was similar to what is seen in Figure 3. Thus, to conserve space equivalent figures for Study 3 are not shown.

The mean pitch matches across subjects showed an average increase, from Session 1 to Session 2, of 207 Hz for the Binary method and 1572 Hz for the Manual method. Paired *t*-tests were calculated to determine if the means between sessions were significantly different for either of the methods. The difference of 207 Hz was not significant for the Binary procedure ($p = 0.6121$), but the difference of 1572 Hz for the Manual procedure was significant ($p = 0.0032$).

Pitch match results of the Subject-Guided method were evaluated two different ways: (1) using only the first of the five pitch matches from each session; and (2) using the average of the five pitch matches made during each session. Paired *t*-tests were calculated to determine if the means between sessions were significantly different. The difference of 171 Hz was not significant for the Subject-Guided (first response) procedure ($p = 0.7325$), and the difference of 497 Hz for the Subject-Guided (average of five responses) procedure was also not significant ($p = 0.1361$).

The next evaluation was to determine individual differences in tinnitus pitch matches between sessions for each method. These difference scores indicated the general trend in direction for pitch matches between Sessions 1 and 2. Each difference score was calculated by subtracting the Session 2 pitch match from the Session 1 pitch match. Thus, a positive difference reflected a higher-frequency pitch match at Session 1 than at Session 2. Conversely, a negative difference reflected a lower-frequency pitch match at Session 1 than at Session 2. The differences varied between positive and negative fairly randomly between subjects for each method. Thus, there was no significant trend for pitch match frequencies to become higher or lower from session to session for any of the methods.

The *absolute values* of the pitch match differences reflect the *magnitude* of each difference, ignoring positive or negative changes in frequency. The absolute values of each between-session difference were calculated, and the across-subjects means of these differences were 1640 Hz (Binary method), 2382 Hz (Manual method), 2351 Hz (Subject-Guided, first response, method), and 1518 Hz (Subject-Guided, average of 5 responses, method). Thus, the Manual method had the largest difference, and the Subject-Guided method (average of five responses) had the smallest difference. A repeated measures ANOVA was calculated across these four means, and there was no significant difference between them ($p = 0.410$).

The final analysis for the different methods was to

calculate Pearson product-moment correlation coefficients between the Session 1 and the Session 2 pitch matches. The Pearson '*r*'s ranged from 0.612 to 0.754 (Table 1). Each Pearson *r* was significant at $p < 0.0001$.

Table 1 Pearson product-moment correlation coefficients for pitch matches between sessions ($p < 0.0001$ for each of the four analyses).

| Binary | Manual | Subject-Guided, 1st Response | Subject-Guided, Average of 5 Responses |
|--------|--------|------------------------------|--|
| 0.807 | 0.641 | 0.596 | 0.785 |

Discussion and Conclusion

A computerized system has been developed to perform fully-automated tinnitus loudness and pitch matching. Loudness matching data have previously been reported, and reliability was seen to be good both within and between sessions (Pearson $r = 0.889$ and $p < 0.0001$ for loudness matching at 13 frequencies) [2]. The present discussion focuses on pitch matching data obtained with the same system, using a variety of techniques.

With the prototype version of the automated system, the method for pitch matching was patterned after the manual method that has been used for over 20 years at the Oregon Tinnitus Clinic, Oregon Health Sciences University. The manual testing conducted at the Oregon Tinnitus Clinic, and the automated protocol patterned after the manual method, both utilized testing methodology starting at 1000 Hz, and stepping up in frequency to gradually approach the frequency of a tone that was closest to a patient's tinnitus frequency. This was a seemingly tedious effort to arrive at a final pitch match which generally occurs in the 4–8 kHz frequency range. To increase the speed of arriving at a final pitch match, two new pitch match procedures were evaluated (Study 2). With the Octave procedure, matching tones started at 1 kHz, but then progressed in octave intervals to rapidly bracket the tinnitus pitch. The Binary procedure started at a middle frequency (4 kHz), and the order of frequencies used for pitch matching bracketed the tinnitus pitch within quartiles of the test-frequency range.

The Binary procedure resulted in more reliable pitch matches than the Octave procedure. Testing with the Octave procedure started at 1 kHz, while the Binary procedure started at 4 kHz. Thus, the Binary procedure eliminated the initial threshold, loudness match and pitch match testing that occurred at frequencies below 4 kHz. Since 4 kHz is in the middle of the frequency range where the majority of tinnitus is reported to be matched, it generally eliminated the time necessary to reach that point in testing. It was expected that this would result in significant time savings, but in fact only

saved about three minutes on average (22 minutes for Binary *vs.* 25 minutes for Octave). Nonetheless, results of pitch match Study 2 revealed a method with improved reliability and shorter testing time.

The average 22 minutes to obtain a pitch match with the Binary procedure was much longer than would be optimal for clinical application. If the final tinnitus pitch match were the only measure necessary, this testing time would not be a problem. However, there are other parameters of tinnitus perception that should also be obtained as part of a tinnitus evaluation battery.

There was further the need to determine if cues were provided by these pitch match procedures that could result in spuriously reliable responses. For both the Octave and Binary procedures, testing started at a fixed frequency and then followed a specific progression of frequency changes according to the subject's responses. It would thus be relatively easy to provide reliable pitch matches from test to test by just repeating the same sequence of responses. There is no reason to believe that the subjects from this study were consciously using such cues to provide responses, but, if a patient desired, such cues would be available with these tests. It is also a possibility that patients who are not skilled at pitch matching might subconsciously use such cues to respond reliably.

In an effort to eliminate the testing cues that could lead to specious responses, and to further shorten testing time, a new pitch match protocol was designed, termed the "Subject-Guided" procedure. With this procedure, testing always started at a test frequency chosen at random by the computer, thus eliminating any possibility of following a fixed order of frequency presentation to produce reliable responses. Another major innovation with this technique was the provision of subject control over rapid changes in frequency to approach and match the tinnitus pitch. Key to that process was maintaining all tone presentations at levels that had been previously matched to the subject's tinnitus loudness [3].

These studies have provided reliability data on four different tinnitus pitch matching protocols. Each protocol seemed to provide reasonable reliability of responses between sessions. The analyses were fairly consistent, however, in that the Binary protocol seemed to show the greatest overall reliability. It is impressive that, using the Binary protocol during Study 3, a Pearson r of 0.807 ($p < 0.0001$) was achieved which indicates a strong correlation between the Session 1 and Session 2 pitch matches from 42 subjects.

It is evident from this analysis that while some subjects were consistent in their pitch match responses, some were clearly inconsistent (see Figure 3). This observation raises the issue of "outliers" when making group comparisons. Unless the raw data are presented, these outliers get ignored in the statistical analyses. Thus, in the present analysis it is not known if there was a normal distribution of variability or if there were an inordinate number of subjects who could not perform reliable pitch

matches. These data will be evaluated carefully and reported in a future publication.

Time of testing was also determined for each method, which is important in determining clinical applicability of a technique. It required an average of 22 minutes to obtain a pitch match with the Binary method, 12 minutes for the Manual method, and 10 minutes for Subject-Guided. With each of these methods, the progression of test frequencies required thresholds and loudness matches to be obtained at each frequency with 1 dB precision. These measurements required the majority of the testing time for these techniques, yet were only used in the process of determining a final pitch match. It should thus be noted that for the Subject-Guided method, the time required to obtain thresholds and loudness matches at each frequency was not factored into the time of testing. Thus, it would take much longer to obtain a pitch match with this method if the total time was added.

For tinnitus pitch matching, if obtaining a pitch match is the only objective, then the time required to determine thresholds and loudness matches in the process must be significantly shortened. For clinical application, the complete evaluation should require no more than about 30 minutes per test ear.

Conclusion

To evaluate treatment efficacy, it is important to provide objective corroboration of a patient's subjective report. There is currently no such objective method recognized for determining tinnitus treatment efficacy, which is problematic when designing outcomes studies for tinnitus therapy. Work is needed to provide techniques that can be advocated for standardized evaluation of tinnitus in outcomes studies. Furthermore, when studying mechanisms of tinnitus in humans (e.g., imaging studies that show areas of brain activity that correspond with tinnitus) a reliable measurement technique would determine the acoustical correlates of tinnitus and show objective evidence of changes that are noted by other, more subjective, methods.

There is a battery of standard audiological tests to evaluate an individual's auditory function. However, no such standard exists for evaluating tinnitus. This is a detriment to both clinical care and research studies related to tinnitus. The present work will hopefully contribute towards establishing standardized methodology for reliably measuring the perceptual attributes of tinnitus.

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Patterns of audiologic findings for tinnitus patients

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Comprehensive diagnostic audiologic assessment is a critical step in the professional management of tinnitus patients. Within recent years, otoacoustic emissions (OAEs) have assumed an important role in the diagnostic audiologic test battery. OAEs offer an objective and highly sensitive clinical measure of cochlear (outer hair cell) function. We report audiologic findings for a series of 225 patients presenting to a medical center audiology clinic with the complaint of tinnitus. In addition to OAEs, the audiologic test battery included measurement of aural immittance, pure tone hearing thresholds, word recognition scores, loudness discomfort levels (LDLs) and, in selected patients, ultra high frequency pure tone audiometry. Tinnitus pitch, loudness and maskability were also determined for all patients. Findings from a comprehensive diagnostic audiologic test battery not only serve to confirm cochlear hearing loss. They also contribute to patient counseling and education and, thus, constitute a definitive step toward successful management of tinnitus.

Methods

Our approach for tinnitus assessment and management is summarized in Figure 1.

Following an in depth consultation, each patient underwent a basic and comprehensive diagnostic audiologic and tinnitus assessment. The test battery consisted of:

- immittance measures (tympanometry, and acoustic reflexes for patients without hyperacusis),
- pure tone audiometry, including interoctave frequencies,
- word recognition scores in quiet,
- distortion product otoacoustic emissions (DPOAE),
- DPOAE and/or TEOAE with contralateral suppression (optional),
- high frequency audiometry (optional),
- loudness discomfort levels (LDLs),
- estimation of tinnitus pitch and loudness,
- maskability of tinnitus (ipsilateral and contralaterally).

Audiologic assessment was supplemented, as indicated, by neurodiagnostic studies. Surgically

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and medically treatable etiologies were ruled out by a neurotologist. Following the audiologic assessment, approximately one-third of the patients elected to pursue an extended tinnitus management program.

Results

Prior to audiologic consultation, the majority of patients were told "... you have normal hearing" and/or "... there's nothing wrong with you" by their primary care physician or a medical specialist. In fact, patients on the average showed at least a mild sensory hearing impairment for some audiometric frequencies (up to 8000 Hz), and abnormal DPOAE findings for some stimulus frequencies within the range of 1000 to 8000 Hz (Figure 2).

In selected patients, high frequency audiometry confirmed abnormal thresholds above 8000 Hz, usually coinciding with the perceived tinnitus pitch. The increased sensitivity of DPOAE versus pure tone audiometry to subtle cochlear deficits is evident in Figure 3.

Perceived tinnitus pitch was correlated with the presence of both audiometric hearing loss and abnormal DPOAE findings. There was, however, no association between the degree of hearing loss or DPOAE abnormality and perceived tinnitus severity. Careful measurement of LDLs contributed to the evaluation of hyperacusis, and provided a baseline measure for documentation of reduced hyperacusis with treatment.

TINNITUS ASSESSMENT AND MANAGEMENT

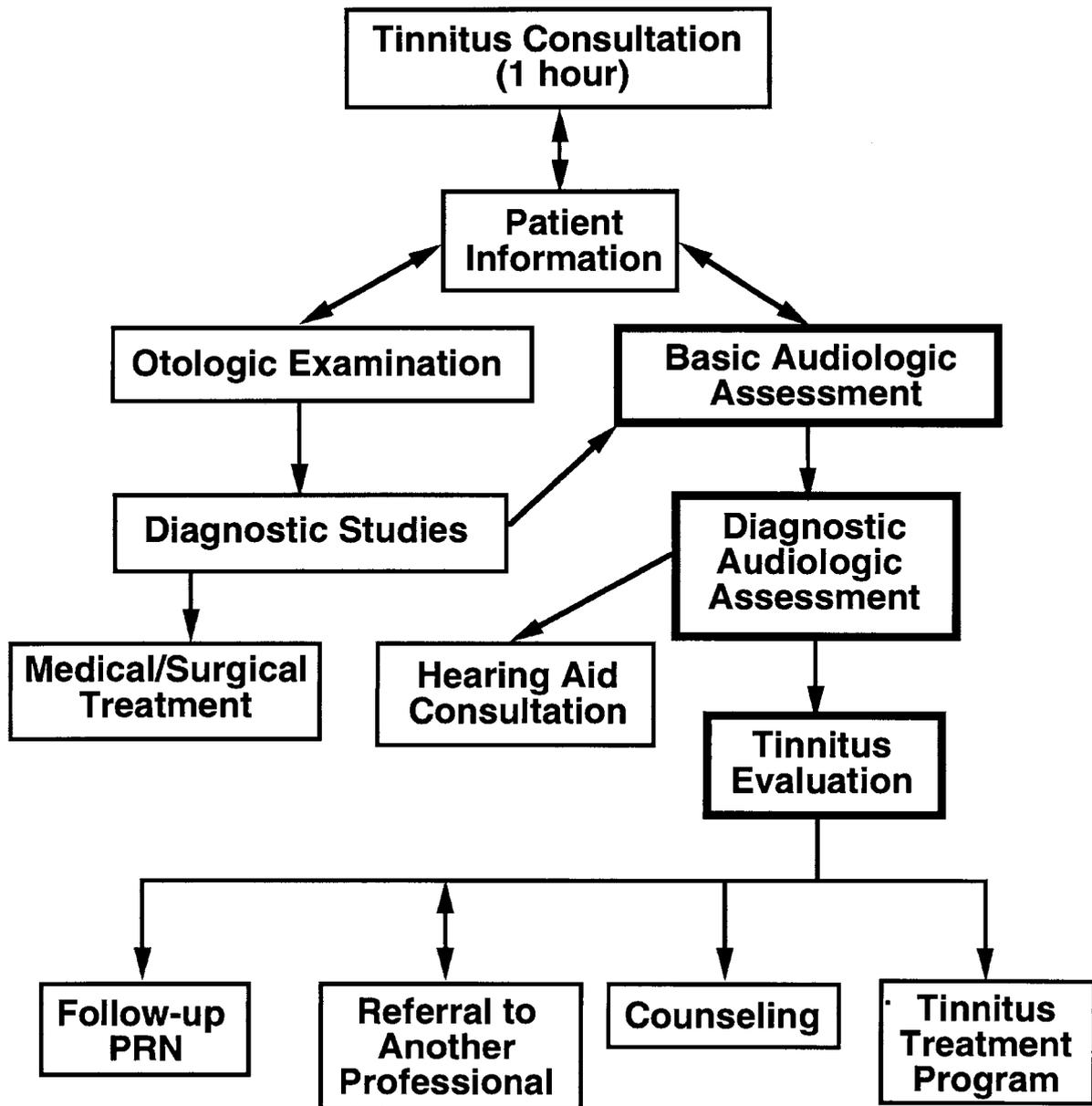


Figure 1

COMPOSITE AUDIOGRAM and DPOAEgram for 236 TINNITUS PATIENTS

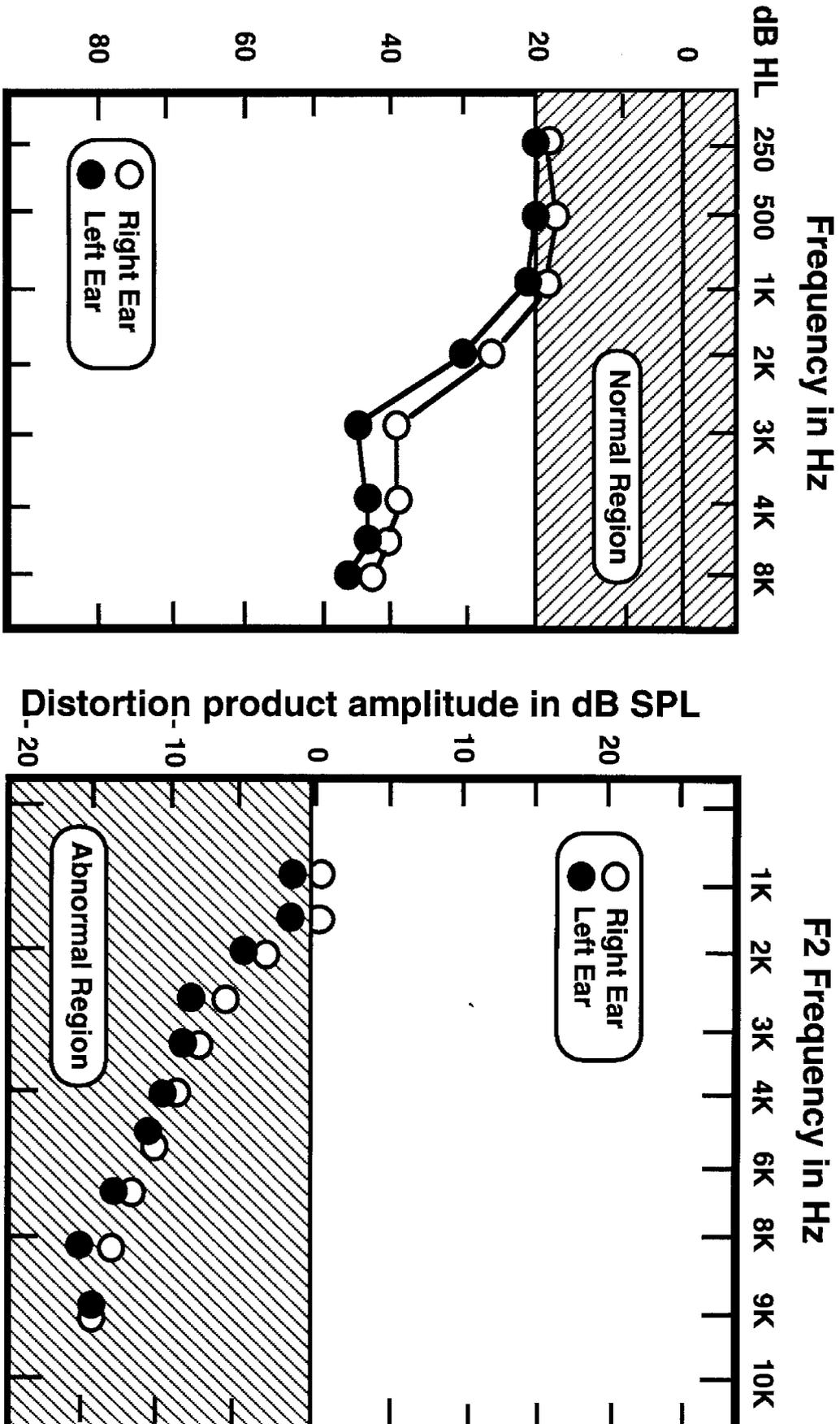


Figure 2

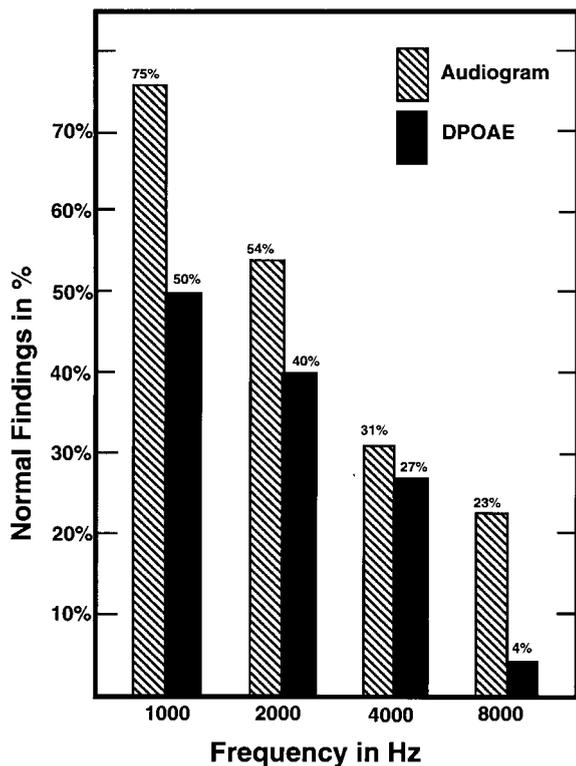


Figure 3

Conclusion

Our results confirm the expected high prevalence of cochlear (outer hair cell) deficits in a tinnitus population. OAEs provide evidence of cochlear dysfunction in virtually all patients complaining of tinnitus, even those with hearing sensitivity within normal limits. Comprehensive audiologic assessment findings contribute not only to accurate diagnosis of auditory dysfunction, and remove the concern of a potentially serious disease process. Findings also are valuable in validating the patient’s tinnitus – in confirming that the patient does have auditory dysfunction that is the likely etiology for their tinnitus. In our experience, OAEs are an essential component in both the diagnosis and management of tinnitus.

Are there psychological or audiological parameters determining tinnitus impact?

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As previous studies showed no correlation between psychoacoustical parameters and distress caused by tinnitus, it seems reasonable to assume that psychological processes are the reason for the extent of tinnitus impact. Therefore it was the aim of our study to determine how patients with a high and low tinnitus impact differ with regard to particular psychological parameters. Our study included 113 patients who underwent an extensive audiological as well as psychological examination. Audiological examination consisted of audiogram and tympanogram, masking curves according to Feldmann, minimum masking level (MML) with white noise, loudness matching and pitch matching. The psychological examination comprised a questionnaire testing stress management and coping strategies (Streßverarbeitungsfragebogen, SVF), the Beck Depression Inventory (BDI), questionnaires testing locus of control (FKK, KKG) and a questionnaire testing tinnitus impact (Goebel and Hiller). In order to work out the differences between patients with high and low distress caused by the tinnitus, our patients were divided into a group with high and a group with low tinnitus impact, according to the results of the tinnitus questionnaire of Goebel and Hiller. Marked statistically significant ($p < 0.01$) differences were observed with respect to illness coping, stress coping as well as locus of control and self-efficacy. There was also a difference in the degree of depression ($p < 0.01$) with patients with high impact showing a higher degree of depression. No differences were noted between the two groups regarding psychoacoustical measurements, with the exception of minimum masking level using white noise which was significantly higher ($p < 0.05$) in the high impact group.

Introduction

Despite many efforts trying to find out what psychoacoustical or psychological parameters are determining tinnitus distress, it still cannot be predicted whether or not a particular patient develops high or low tinnitus distress. However it seems that the main factors influencing tinnitus impact cannot be characterised by psychoacoustical parameters as they are not – or only weakly – related to tinnitus distress as self-reported or measured with tinnitus severity questionnaires [1,2]. In many publications, however, psychological parameters have been reported to change with tinnitus distress [3,4,5].

Andersson and McKenna (1998) [6] as well as other authors [7,8] have stressed the importance of the degree of depression as measured with the Beck

depression inventory for the tinnitus severity. The locus of control, which means the extent to which the patient perceives events to be under his own control, has been discussed in publications by Budd and Pugh (1995) [5] as well as Attias *et al.* (1995) [3]. Attias *et al.* [3] showed that help-seeking tinnitus patients had an external locus of control and non-help-seeking patients an internal locus of control. This means that patients seeking for help attributed success to factors beyond their own control while non-help-seeking individuals attributed successful outcomes to their own effort. Budd and Pugh (1995) [5] found locus of control not to be correlated directly with tinnitus severity when using partial correlations but being correlated with the degree of depression, which in turn was correlated with tinnitus impact. Locus of control should be of particular importance as Craig *et al.* (1984) [9] stated that patients with internal locus of control are motivated to use coping strategies, while patients with external locus of control tend not to make use

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of positive coping strategies. However, in most publications, no distinction has been made between locus of control with respect to the disorder and general locus of control which can be altered by learning processes. Coping with stress has also been a subject of research in a number of publications [10,11] showing ways of coping to change with tinnitus distress. Again in most publications no distinction was made between general coping with stress and coping with illness in particular.

It was the purpose of the present study to examine the above-mentioned parameters such as degree of depression, locus of control and coping with stress in one single study together with psychoacoustical parameters. Since general locus of control and locus of control with respect to the disorder are not necessarily the same just as general ways of coping and coping with a particular disorder are not necessarily the same we examined these parameters separately. By measuring a broad spectrum of psychological as well as psychoacoustical parameters in the same patients it seemed possible to obtain information about correlations of a wide spectrum of parameters and particularly to find out in what parameters patients with high and low tinnitus impact differ. This enabled us to generate more specific hypotheses about processes leading to a high tinnitus impact.

Materials and Methods

One hundred and thirteen patients (73 male, 40 female) were included in the study. Patients were between 16 and 73 years old with a mean age of 47 years. All patients suffered from chronic tinnitus which had lasted for at least 3 months. In all patients an audiological as well as a psychological examination was performed following a microscopic inspection of the ear drums.

Audiological examination

Audiogram: pure tone thresholds were measured in the standard frequencies between 125 and 10000 Hz in 1 dB steps using a computer audiometer (Dorn, Germany)

Feldmann curves: masking curves according to Feldmann were recorded using narrow band noise with centre frequencies corresponding to the frequencies of the pure tone thresholds.

Minimal Masking Level: Minimal masking level was measured using white noise. The noise was applied ipsilaterally and contralaterally

Tinnitus pitch measurements: tinnitus pitch was measured as the frequency of a pure tone corresponding most closely to the predominant pitch of the tinnitus. In order to do this a two-alternative forced-choice method was used.

Tinnitus loudness: tinnitus loudness was measured at the frequency of the tinnitus using pure tones in patients with a tonal tinnitus and a narrow band noise or a white noise in patients where these sounds corresponded closely to the tinnitus. Before

loudness matching, the threshold was remeasured using a pure tone stimulus, a narrow band noise or a white noise with 1 dB resolution. The external stimulus was presented on the ipsilateral and the contralateral ear. Loudness of the external signal was increased until the patient reported that the loudness exceeded the loudness of the tinnitus. Then loudness was decreased until it was just below the loudness of the tinnitus. By then increasing the loudness of the external signal in 1 dB steps, a loudness match was obtained.

Psychological Evaluation

Beck Depression Inventory: In order to measure depression in our tinnitus patients the Beck depression inventory [12] was applied. This questionnaire can be seen as a standard instrument and has been used in a large number of studies. We used the German version of this questionnaire published by Hautzinger *et al.* (1995) [13].

Stress coping questionnaire (SVF) [14]: In order to obtain information about strategies of coping with stress used by tinnitus patients the questionnaire by Erdmann *et al.* (1984) was used.

Illness coping questionnaire (Freiburger Fragebogen zur Krankheitsverarbeitung; FKV) [15]: This questionnaire consists of 142 items and measures 27 scales representing ways of coping with chronic illness.

Questionnaire testing self-efficacy and locus of control (LOC) (FKK) [16]: This questionnaire tests the general self-efficacy of the patients which means the extent of their general belief that they are able, even in difficult and new situations, to control the situation. On the other hand the test measures locus of control with separate scales for internal, external (powerful others) and chance control.

Illness locus of control (KKG) [17]: This questionnaire measures the illness locus of control also with separate scales for internal and external LOC with respect to a particular disorder.

Tinnitus questionnaire [18]: In order to measure the degree of distress caused by the tinnitus, the tinnitus questionnaire of Goebel and Hiller – which is a German version of the tinnitus questionnaire by Hallam (1988) [19] – was used. Like the Hallam questionnaire [19] it consists of 52 items. Apart from the main scale of the questionnaire, which measures the general tinnitus impact, the test measures a number of subscales such as psychological distress (emotional and cognitive) tinnitus intrusiveness, audiological perceptual difficulties, sleep disturbances and somatic complaints.

Results

Tinnitus grading [18]

Main score: Tinnitus impact was measured using the tinnitus questionnaire of Goebel and Hiller, which is a German version of the tinnitus questionnaire by Hallam. In this questionnaire a score ranging from 0 to 84 is possible. A score ranging

from 0 to 30 corresponds to grade 1 (low impact), a score from 31 to 46 to grade 2 (moderate impact), a score from 47 to 59 to grade 3 (high impact) and from 60 to 84 to grade 4 (maximum tinnitus impact). According to this grading 31 patients showed grade 1, 37 patients grade 2, 36 patients grade 3 and 29 patients grade 4. For further evaluation patients showing grade 1 and 2 are called "low impact patients", patients with grade 3 and 4 "high impact patients".

Audiometric measurements

Hearing function: No significant difference regarding hearing function was seen when comparing patients with high and low tinnitus impact.

Feldmann masking curves: No significant difference could be seen when comparing the different types of Feldmann curves with respect to tinnitus impact.

Minimal Masking Level: Comparing patients with high and low tinnitus impact, a statistically significant difference was observed regarding minimal masking levels with white noise when the noise was applied ipsilaterally as well as contralaterally.

Tinnitus pitch measurements: Mean frequencies corresponding to the tinnitus pitch were 5909 ± 2964 Hz in patients with high tinnitus impact and 5019 ± 2842 Hz for patients with low impact showing a tendency of the patients with high tinnitus impact to have a higher tinnitus pitch. However because of the high standard deviation this result is far from being statistically significant.

Tinnitus loudness: No significant difference could be found regarding tinnitus loudness when comparing patients with high and low tinnitus impact. This is true for measurements in dB HL and dB SL.

Psychological testing

Beck Depression Inventory: For all patients combined the mean score was 11.4 ± 7.4 which shows the existence of mild to moderate depression symptoms. The Beck depression scale showed statistically highly significant ($p < 0.01$, student t-test) differences when comparing patients with high and low tinnitus impact. The mean score in high impact patients was 14.5 ± 8.1 compared to 7.6 ± 4.7 in the group with low tinnitus impact. The depression scores in the low impact group were therefore more or less in the normal range whereas in the high impact group the mean score was similar to that of patients with chronic pain. There was a significant correlation ($p < 0.001$) between the Beck depression inventory main score and the main score in the tinnitus questionnaire ($r = 0.55$).

Stress coping questionnaire [14]: The tinnitus patients observed in this study showed ways of coping that are generally similar to those observed in a normal population [14]. Remarkable differences however are found with the coping strategies "denial of guilt", "need of social support" and "social isolation". When comparing high and low

impact patients, significant differences could be found with respect to "resignation", "self-blame" and "drug intake" with high impact patients exhibiting these ways of coping to a higher extent.

Questionnaire testing general locus of control and self-efficacy (FKK) [16]: A comparison of the total population in this investigation with a normal population shows that these two groups do not differ with respect to the degree of internal locus of control, external locus of control and self-efficacy. Patients with low and high tinnitus impact differ significantly with respect to self-efficacy which means that patients with low tinnitus distress think that they can generally solve most problems. People with high tinnitus impact are generally self-conscious and think that they are likely not to manage new situations in the right way. Also tinnitus patients with low and high distress differ significantly with respect to the scale "internal versus external LOC" showing that more high impact patients have an external LOC whereas low impact patients tend to show an internal LOC.

Health and illness locus of control (KKG) [17]: Patients with high and low tinnitus impact do not differ in their health and illness locus of control.

Illness coping questionnaire (FKV) [15]: Statistically significant differences were seen with respect to the subscores "problem focussed coping", "depression", "hedonism", "pessimism", "avoidance" "social isolation" and "regressive tendencies".

Principal Component Analysis

In order to obtain more clarity about the processes leading to a high tinnitus impact, a principal component analysis of all psychological and psychoacoustical data was performed using the software package SPSS. The analysis resulted in the extraction of 8 factors accounting for 51.97% of the total variance. The interpretation of more factors was not considered reasonable as they did not contain factor loadings above 0.35 which is the smallest factor loading to be interpreted in the given sample size. As only 2 factors contain variables that are significantly different when comparing patients with high and low tinnitus impact, only these factors – together with one with a high eigenvalue – are described more closely.

Factor 1: Factor 1 has an eigenvalue of 30.68 and accounts for 20% of the total variance. The variables included in factor 1 are shown in Table 1. They are a number of maladaptive strategies of coping with stress as well as strategies of coping with illness. Also data from the self-efficacy and locus of control questionnaire are included in this factor, with self-efficacy having a negative factor loading and external locus of control having a positive factor loading (Table 1). Because many of the variables mentioned above show significant differences when comparing patients with high and low tinnitus impact, it seems obvious that this factor plays a role in the extent of tinnitus impact. It contains a number of variables representing maladaptive strategies

of coping with stress such as “resignation” and “self-pity”. On the other hand patients with high factor scores generally have a low self-efficacy, an external locus of control and a high degree of depression. Thus the variables in factor 1 represent a chain of psychological processes and beliefs that are likely to increase tinnitus distress. Possible mechanisms for this are discussed below.

Factor 2: Factor 2 which accounts for 9.3% of the total variance, contains variables of the stress coping questionnaire (SVF) with a factor loading of 0.5 to 0.6. The variables with their corresponding factor loading are shown in Table 1. This factor consists – apart from other variables – of somewhat more positive coping with stress.

It also contains a number of variables from the illness coping questionnaire with factor loadings from 0.6 to 0.7. Generally this factor represents more positive coping mechanisms. As none of the variables show statistically significant differences when comparing high and low impact patients, it can be concluded that this factor only plays a minor role in determining tinnitus distress.

Factor 3: This factor is determined by the main score and all subscores of the tinnitus questionnaire of Goebel and Hiller as well as the main score of the Beck depression inventory. Interestingly, the minimal masking level using white noise also is included in this factor. The factor loadings are shown in Table 1. As the variable with the highest factor loading in this factor is the main score of the tinnitus questionnaire of Goebel and Hiller, this factor can be named “tinnitus distress factor”.

Of the factors described below only factor 1 and 3 contain variables that show significant differences

when comparing patients with high and low tinnitus impact. Therefore it can be said that these factors play a major role in determining the degree of tinnitus impact whereas the others do play only a marginal role if at all. The most important factor, however, is factor 1, containing most of the variables changing with tinnitus distress. Few of these variables have not only a high factor loading in factor 1 but also have a moderate factor loading in factor 3 which we have named “tinnitus distress”. The strongest of these variables is the main score of the Beck depression inventory. One possible interpretation of this fact is, that this factor acts as a “link” between factors 1 and 3. In other words, it may be that depression is one link in the chain of psychological processes represented by factor 1 consecutively influencing processes represented by factor 3 (tinnitus distress).

Discussion and conclusion

In our study, we were able to show that patients with high and low tinnitus impact differ in a number of psychological parameters and only little in psychoacoustical parameters. This finding supports the results of several earlier studies [1,20]. The only significant difference with respect to psychoacoustical parameters was found when comparing the minimal masking levels using white noise in patients with high and low tinnitus distress. This finding can be interpreted according to the neurophysiological model of tinnitus as a “measure of detectability of the tinnitus signal from the background neural activity” [21]. This means that patients with high

Table 1 Variables and factor loadings of factors 1, 2 and 3. Numbers represent the factor loadings

| | Tinnitus grading | Stress coping | Beck depression inventory | Locus of control and self-efficacy questionnaire | Illness coping questionnaire | Psychoacoustical measurements |
|-----------------|------------------|--|---------------------------|--|---|-------------------------------|
| <i>Factor 1</i> | | Resignation (0.81) Mental perseverance (0.66) Self-pity (0.64) Social isolation (0.61) Escapism (0.56) Drug intake (0.5) | Main score (0.6) | Powerful others control (0.6) Chance control (0.5) Self-efficacy (-0.74) | Depression (0.57) | |
| <i>Factor 2</i> | | Search for self-approval (0.67) Reaction control Positive self induction (0.62) Playing down (0.58) Distraction (0.53) Situation control (0.52) | | Internal control (0.62) | Self-assurance (0.58) Hedonism (0.57) “playing down” by comparison (0.53) Problem focussed coping (0.51) | |
| <i>Factor 3</i> | Main score (0.6) | | Main score (0.42) | | | MML (white noise) |

tinnitus distress are able, as they focus their attention maximally to the tinnitus signal, to detect this signal even from a high background neural activity as evoked by the white noise.

The most pronounced differences between patients with high and low tinnitus distress existed for psychological parameters. The main score of the Beck depression inventory [13] was 11.4 ± 7.4 indicating a mild degree of depression similar to that in patients with chronic pain [13]. Erlandson [22] reported a similar degree of depression (mean value of 13.3 ± 8) in tinnitus patients. As there is a correlation of 0.5 between the tinnitus questionnaire main score and the BDI main score, it can be suspected that the degree of depression influences tinnitus impact, a claim several earlier publications have made [5,6].

As mentioned above, the general locus of control (internal or external) has been shown to change with tinnitus severity [5]. This finding is supported by our data showing that patients with high distress tend to have an external locus of control. Also patients with low tinnitus distress exhibit a higher degree of self-efficacy. This means that tinnitus patients with high distress generally think that they cannot influence the disorder. As a consequence of this belief they do not apply effective coping with their disorders, which results in high tinnitus impact. When calculating partial correlations however, we and others [5] were not able to show direct correlations of general locus of control and tinnitus distress but found that the degree of external locus of control shows a partial correlation with the degree of depression measured by the main score of the Beck depression inventory, which in turn shows correlation with tinnitus impact. It has been shown [23] that the general locus of control is not always the same as the illness locus of control and that illness locus of control can be seen as a result of a learning process concerning a particular disorder. Considering this it can be concluded that locus of control with respect to tinnitus is the result of obtaining information about tinnitus and of experiences they make with the tinnitus or the treatment of the tinnitus. As experiences with tinnitus therapy are largely equally negative and the sources of information about tinnitus are basically the same for all tinnitus patients, it seems clear that the locus of control that develops is similar in all patients. Accordingly tinnitus patients in our study do not differ with respect to the illness locus of control. The fact that the locus of control with respect to the disorder is different from the general locus of control supports the suspicion that general locus of control is not directly influenced by the tinnitus itself, and that general locus of control might be pre-existent and thus one of the variables determining whether a high or low degree of tinnitus distress develops.

Major differences between high and low impact patients were seen regarding strategies of coping with stress and coping with illness. Tinnitus patients with high tinnitus impact tend to exhibit coping strategies that are maladaptive to a much higher

degree than patients with low tinnitus impact. Dineen *et al.* (1997) [10] found that coping strategies in their population were influenced by the beliefs the patients held about tinnitus. This is also the case in our patients as strategies of coping with stress and beliefs about tinnitus are both part of factor 1 which influences tinnitus impact by an increase of depression and possibly other, not yet investigated variables. Using the ways of coping checklist Attias *et al.* (1995) [3] found significant differences between help-seeking and non-help-seeking patients with tinnitus with respect to "problem-focussed coping", "emotional-focussed coping" and "distancing coping". However, contrary to the above mentioned findings, we differentiated between general coping with stress and coping with illness. In both questionnaires we observed differences when comparing high and low impact patients. This fact suggests major importance of coping with stress and illness in the development of tinnitus distress. However we consider coping with stress not a primary, pre-existent variable in the cascade of psychological processes leading to tinnitus distress. Rather it seems to be that strategies of coping with stress and illness are chosen depending on the general locus of control and self-efficacy and result in a corresponding degree of depression which in turn influences tinnitus impact. Of course the mechanism suggested here is only one – though possibly an important – part of the wide variety of psychological processes leading to high tinnitus distress.

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Changes in spontaneous firing activity of cortical neurons in adult cats after mild to moderate pure tone trauma induced at 5 weeks of age

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The chronic effect of pure tone trauma on single-unit firing activity in the primary auditory cortex was investigated in five cats. The cats were exposed to loud pure tone presented from a speaker for 1 hour at 126 dB SPL at 5 and 6 weeks of age. The trauma-tone frequency was 6 kHz. Recordings were performed between 7 and 16 weeks after exposure. In traumatized cats ABR thresholds increased by about 30 dB relative to those in normal cats for frequencies above 12 kHz.

Spontaneous activity between normal areas and reorganized areas was compared. Spontaneous firing rates were significantly higher in reorganized areas (mean = 2.2, SD = 1.3 sp/s) than in normal areas (mean = 1.25, SD = 0.85 sp/s). We also compared the traumatized cats with a large group of normal ones. In normal cats, spontaneous firing rates in 363 single units were independent of CFs (Mean = $1.34 + 0.006 \times \text{CF}$ (kHz), $R^2 = 0.001$), however, in traumatized cats spontaneous firing rates increased significantly with CF (Mean = $0.36 + 0.181 \times \text{CF}$, $R^2 = 0.158$). The rate of burst occurrence, burst duration, number of spikes in a burst, and percentage of spikes in bursts between normal and reorganized cortical area was compared and no significant differences were found. In order to test the hypothesis that reorganized cortex might show higher synchronization of spontaneous activity, cross-correlation analysis was done on 140 single-unit pairs recorded in the traumatized cats. The single electrode pair correlations were not dependent on CF and not significantly different for normal and trauma areas. For the dual-electrode correlations that were significantly different from zero, there was no significant difference in peak cross-correlation coefficients for the firings of simultaneously recorded cells between normal (mean = 0.015, SD = 0.009) and reorganized areas (mean = 0.019, SD = 0.023). From the 84 dual-electrode pair cross-correlations evaluated in the normal frequency region 58 were significant different from zero, whereas in the trauma region all 56 recorded were significant. This suggests a potential effect of cortical reorganization on spontaneous neural synchrony.

Thus both changes in spontaneous firing rate and in firing synchrony might be related to the tinnitus that frequently accompanies high frequency hearing loss induced by noise trauma.

Introduction

It is known that noise trauma induces hearing loss with tinnitus. Potential neural substrates of tinnitus in the auditory cortex are increased neural spontaneous firing rate and/or an increase in neural synchrony. In a previous study, it was found that spontaneous firing rate was increased significantly in the primary auditory cortex (AI) in cats up to at

least 5 h after induced pure tone trauma [1]. In this study, we investigate spontaneous firing activity and synchrony between single units in AI in cats between 7 and 16 weeks after pure tone trauma was induced at 5 weeks of age.

Methods

Animals

Five cats were exposed to a 6 kHz tone of 126 dB SPL for 1 hour at 5 weeks of age and again at 6 weeks of age. Recordings were performed between 7 and 16 weeks after exposure. Seven age-matched control cats were used for comparison.

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Animal preparation

All cats were premedicated with 0.25 ml/kg body weight of a mixture of 0.1 ml acepromazine (0.25 mg/ml) and 0.9 ml of atropine methyl nitrate (5 mg/ml) subcutaneously. After about one-half hour they received an intramuscular injection of 25 mg/kg of ketamine hydrochloride (100mg/ml) and an intraperitoneal injection of 20 mg/kg of sodium pentobarbital (65mg/ml). Under local anesthesia, the skin was removed and a small hole was trephined over the right auditory cortex. Additional acepromazine/atropine mixture was administered every 2 hours. Light anesthesia was maintained with intramuscular injections of 2–5 mg/kg/hour of ketamine. The temperature of the cat was maintained at around 37°C with a thermostatically controlled blanket (Harvard Medical System). At the end of the experiment the animals were sacrificed with an overdose of sodium pentobarbital.

Peripheral hearing test

Auditory brainstem responses (ABR) were recorded with needle electrodes in the muscles overlying the two mastoids. Thresholds were obtained for short tone-pips with frequencies between 2 and 20 kHz and presented at a rate of 10 Hz. In control cats the ABR thresholds were on average 20 dB higher than the multi-unit neural thresholds in AI.

Acoustic stimulus presentation

The place-frequency map in AI was determined by determining characteristic frequencies (CF) and tuning properties of the individual neurons using tone-pips with frequencies between 625 Hz and 40 kHz presented at a rate of 1 Hz. After that, 15 minutes of spontaneous activity was recorded.

Recording and spike separation procedure

Three tungsten micro electrodes with impedances between 1.5 and 2.5 M were independently advanced perpendicular to the primary auditory cortex surface and approximately orthogonal to the iso-frequency bands. Recording bandwidth was between 200–3000 Hz. The multi-unit electrode signals were separated into single-unit spike trains using a maximum variance algorithm [2].

Data analysis

Spontaneous firing rate, CF, burst properties and peak cross-correlation coefficients were calculated using Stranger[®] software. All statistical analyses were performed using StatView 5[®].

Results

Forty-two multi-unit recordings resulting in 225 single units in primary auditory cortex of traumatized cats were analyzed. For comparison purposes,

we also used data from 363 single units in primary auditory cortex recorded in a large group of normal cats. 140 single-unit dual-electrode pairs recorded in the traumatized cats were used for cross-correlation analysis.

In traumatized cats ABR thresholds were increased by about 30 dB relative to those in control cats for frequencies above 12 kHz.

Spontaneous firing rates in trauma cat ears were significantly higher in reorganized areas (mean = 2.2, SD = 1.3 sp/s) than in normal areas (mean = 1.25, SD = 0.85 sp/s), largely because a lack of firing rates below 1 spike/s (Figure 1a). In control cats, spontaneous firing rates were independent of CFs (Mean rate = $1.34 + 0.006 \times \text{CF}$ (kHz), $R^2 = 0.001$), however, in traumatized cats spontaneous firing rates increased significantly with CF (Mean rate = $0.36 + 0.181 \times \text{CF}$, $R^2 = 0.16$).

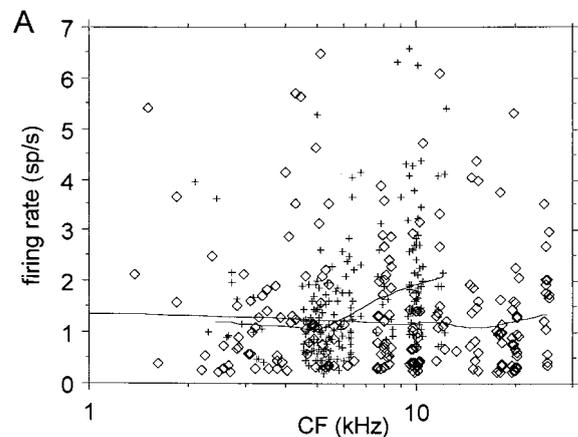


Figure 1a Spontaneous firing rate in trauma ears. This figure shows dependence of spontaneous firing rate on CF for trauma ears and control cat ears. Locally weighted average curves are drawn in.

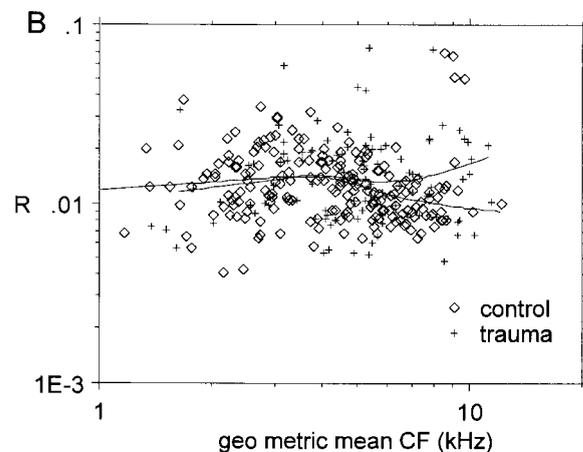


Figure 1b Dual-electrode pair cross correlation coefficients. This figure shows dependence of the peak cross-correlation coefficient (logarithmic coordinates) on the geometric mean of CFs of the individual neurons. The data points for normal and trauma regions represent those that are significantly different from zero.

We compared the rate of burst occurrence, burst duration, number of spikes in a burst, and percentage of spikes in bursts between the normal and the reorganized cortical areas and found no significant differences. No dependence on CF in the trauma cats was found. Thus, no change in the temporal aspects of spontaneous firing was found.

For the firings of simultaneously recorded neurons on separate electrodes, there was no significant difference in peak cross-correlation coefficients between normal (mean = 0.015, SD = 0.009) and reorganized areas (mean = 0.019, SD = 0.023), provided that only peak correlation coefficients that were significantly different from zero were used. From the 84 dual-electrode pair cross-correlations evaluated in the normal frequency region 58 were significant different from zero, whereas in the trauma region all 56 recorded were significant.

Conclusions

(a) Spontaneous firing rates in AI were significantly higher in reorganized areas than in areas with normal topography.

(b) In contrast, the mean strength of the neural synchrony was not changed. However, in the

trauma region, all dual-electrode pair cross-correlations were significant different from zero, whereas in the normal region only 72% of the correlations were significant.

(c) These findings are potentially related to the occurrence of tinnitus following exposure to loud sounds: reorganization of cortical topographic maps following noise trauma, changes both in spontaneous firing rate and the occurrence of neural synchrony.

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Modification of single-unit activity related to noise-induced tinnitus in rats

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Delineating the tinnitus-related neuronal activity is of crucial importance for understanding the mechanisms of tinnitus. The recent development of an animal model, based upon noise-induced tinnitus and hearing loss, allowed for the study of the correlation of the parameters of the spontaneous neuronal activity to the extent of the behavioral manifestation of tinnitus. Details of our animal model of noise-induced tinnitus are presented in a separate presentation. Briefly, anesthetized rats were exposed unilaterally for 20 min to 110 dB SPL, 7.8 kHz pure tone at the proper stage of the behavioral paradigm. Animals which were not exposed to sound, but underwent the same behavioral procedure, were used as a control. To separate the effects of hearing loss from those of tinnitus, unilateral conductive hearing loss was induced by removal of the tympanic membrane in a separate group of rats.

Recordings of spontaneous and evoked activity of single units were performed from the external and dorsal parts of the inferior colliculus after completing the behavioral procedures. Five minutes of spontaneous activity was recorded and the units were classified according to their responses to sound stimulation. Mean frequency of discharges and interval histograms were constructed. Furthermore, the spontaneous activity of each unit was evaluated using the Poisson surprise method which identified bursts of activity, that were significantly divergent from the remaining activity. Units were classified according to their types of response and their characteristic frequency. Their bursting activity was characterized and correlated with the behavioral manifestation of tinnitus.

The results showed that bursting activity is prevalent in rats with noise-induced tinnitus, but not in control rats, and animals with unilateral conductive hearing loss. Furthermore, the probability of bursting activity is higher for units with characteristic frequency within the range of maximal damage to the cochlea, as assessed by distortion product otoacoustic emission and frequency specific auditory brainstem response. Notably, there is a clear correlation between various parameters of bursting activity and the extent of the behavioral manifestation of tinnitus. These results are consistent with our previously reported results with salicylate-induced tinnitus, and strongly suggest that this bursting type of activity might be the neuronal basis for tinnitus. However, this type of activity could not be detected by methods aimed at evaluation of changes of the metabolic activity (such as 2-deoxyglucose, PET, SPET, fMRI) if not accompanied by an overall significant increase of activity. Since the mean rate of the spontaneous activity showed only a moderate increase in sound exposed animals as compared to controls, it is unlikely that these methods would be helpful in detecting of the tinnitus-related bursting activity.

Introduction

There is a consensus that delineating tinnitus-related neuronal activity is of crucial importance for understanding the mechanisms of tinnitus. The data related to this issue has increased significantly during the past few years. An increase of spontaneous activity in the dorsal cochlear nucleus of

animals exposed to high levels of sound has been documented [1]. Also, modification of single unit activity in auditory cortical areas A1 and A2, have been shown to result from salicylate and quinine application [2]. Results from our group showed a slight increase in the average spontaneous activity recorded from the inferior colliculus of rats after administration of salicylate [3]. However, the dominant change observed in our experiments has been the emergence of an abnormal, high frequency, epileptic-like, burst-type activity.

Recently, we have proposed a modified animal model of tinnitus in which tinnitus and hearing loss

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are induced by exposure of animals to high levels of sound rather than by administration of salicylate or quinine. This model, outlined in an accompanying paper [4], allows for the independent assessment of hearing loss, functioning of the outer hair cell system, and tinnitus, separately for each individual rat. Therefore, it represents a convenient tool to assess the changes in the neuronal spontaneous activity which may potentially be related to tinnitus and/or hearing loss.

Method

A total of 74 pigmented rats were used in this study. The sound-exposed group consisted of 38 rats, exposed unilaterally for 20 min at 110 dB SPL, 7.8 kHz pure tone under Nembutal anesthesia. The exposure was performed after the second day of Pavlovian suppression training [5]. Following one day of recovery the rats were tested during seven days of passive extinction. The control group ($n = 36$) underwent the same behavioral procedures but without sound exposure. After completion of behavioral testing, the frequency-specific ABR, and the distortion product otoacoustic emission (DPOAE) were evaluated. Frequency specific ABR were obtained for frequencies of 2–16 kHz, with the resolution of 1/3 octave. The DP measurements were performed for sound levels of 45, 55, and 65 dB SPL of L1 ($L2 = L1 - 10$ dB), within the frequency range of 2–16 kHz, 10 points per octave. 300 s of single unit spontaneous activity has been recorded from the external nucleus of the inferior colliculus, followed by evaluation of unit characteristic frequency (CF), and the evoked activity. Cambridge Electronic Design Spike 2 software was used for isolating individual spikes and for subsequent analyses.

Our results from single unit recordings in animals with salicylate-induced tinnitus demonstrated the presence of abnormal bursts of activity [5]. These bursts were detected using specifically prepared programs that identified a train of intervals with each interval within a given range of duration. This approach, however, was not based on any statistical methods. To assure the statistical identification of the bursting activity the Poisson surprise method [6] has been used.

In this method the statistical measure used is $S = -\log P$; where P is the probability that, in a random (Poisson) spike train, having the same average spike rate r as the spike train studied, a given time interval of length T contains n or more spikes. P is given by Poisson's formula as $P = \exp(-rT) \sum_{i=n}^{\infty} (rT)^i / i!$ with a summation for $i = n$ to ∞ [6]. The method identifies a sequence of spikes, which has a given level of probability to occur due to random fluctuation. For example, for $S = 6$, the probability that a given series of spikes to occur spontaneously is $P = 10^{-6}$, e.g., one in a million.

Results

The behavioral evaluation of rats exposed to 110 dB SPL pure tone revealed significant facilitation of the extinction process, as compared with the control group (not shown). Exposure to sound resulted in a damage to the cochlea, as manifested by DPOAE shift, predominantly in the area of 5 to 15 kHz (ABR data are consisted with DPOAE).

A total of 410 units, for which CF has been found, were recorded from 29 rats, with 180 units recorded from control (8 rats), and 230 (21 rats) from sound exposed animals. The average rate of spontaneous activity in sound exposed animals was significantly higher as compared with control (mean \pm SEM: 10.51 ± 1.25 , $n = 190$ vs. 8.36 ± 1.10 , $n = 168$, NS).

On the basis of the DPOAE and ABR findings the units were grouped into three ranges depending on their characteristic frequency: A—CF below 5.5 kHz, with no significant damage to the cochlea; B—CF between 5.5 and 15.5 kHz, with largest damage documented; and C—CF higher than 15.5 kHz, with less or, in some rats, absent damage. Evaluation of the spontaneous activities within these three ranges revealed that only units with CF in the range corresponding to cochlear damage exhibited significant increase. Specifically, the means for sound exposed versus control group, were for range of CF below 5.5 kHz 7.44 ± 1.03 , $n = 50$ vs. 5.97 ± 1.06 , $n = 23$, (NS); for CF between 5 and 15 kHz 13.17 ± 1.04 , $n = 109$ vs. 9.89 ± 1.1 , $n = 77$ ($p < 0.05$); and for CF above 15 kHz 10.93 ± 1.69 , $n = 31$ vs. 9.23 ± 1.13 , $n = 68$ (NS). Note, that the only significant difference between sound-exposed and control groups emerged for frequency range corresponding to cochlear damage.

For the Poisson surprise the value $S = 9$ yielding the probability of activity in the burst less than 10^{-9} was selected on the basis of the literature [6]. Initial characterization of the bursting activity has been performed by evaluating average number of bursts per unit, number of spikes in a burst, and percentage of time the activity is contained in these bursts. Statistical evaluation revealed that, for number of bursts and percentage of time, the sound exposed group exhibited significantly higher values for frequency range corresponding to maximal damage of the cochlea, (number of bursts: 6.08 ± 0.78 , $n = 129$ vs. 2.94 ± 0.44 , $n = 78$, $p < 0.01$; percentage of time: 5.16 ± 0.53 vs. 2.94 ± 0.59 , $p < 0.001$), and difference was at the borderline of significance for number of spikes per burst (43.77 ± 3.98 vs. 32.98 ± 4.04 , $p = 0.06$). The differences for other frequency ranges were not statistically significant.

Our results obtained while establishing the animal model of sound-induced tinnitus show that there is only a weak correlation between the hearing loss and the manifestation of tinnitus. This finding has been confirmed by this study. An analysis of the behavioral manifestation of tinnitus [7] as a function of the mean hearing loss revealed no significant correlation ($n = 17$, $p = 0.43$, NS; Figure 1). It is to be noted that rats with the same extent of hearing

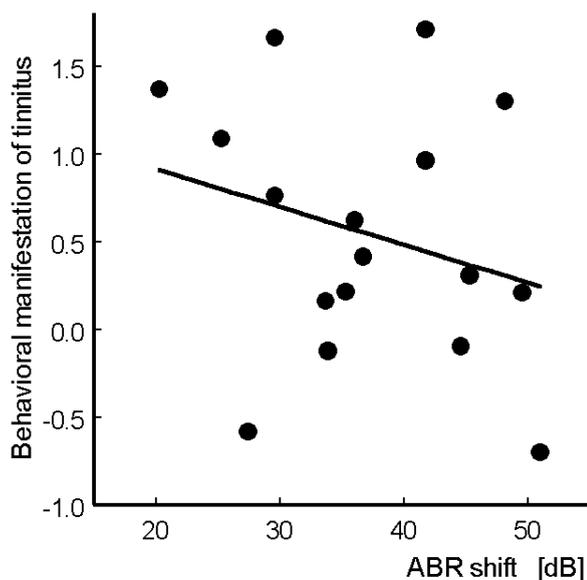


Figure 1 Correlation of the behavioral manifestation of tinnitus with the mean hearing loss. Note lack of a significant relationship.

loss can differ dramatically in their behavioral manifestation of tinnitus, and rats with a similar behavioral manifestation of tinnitus can have distinctively different amounts of the hearing loss.

Our previous results indicated that bursting activity might be related to the behavioral manifestation of tinnitus but not to the hearing loss. Consequently, correlation analyses were performed, in which the parameters of the bursting activity have been correlated with the behavioral manifestation of tinnitus, and with mean hearing loss. The bursting activity turns out to be correlated only with the behavioral manifestation of tinnitus for units with frequency range corresponding to maximal damage to the cochlea (Figures 2–4). There was no correlation for units with CF belonging to other frequency ranges (not shown). Finally, bursting activity was not correlated with hearing loss for any of frequency ranges.

Discussion

As evident from these results, there is a highly significant correlation between bursting activity and the behavioral manifestation of tinnitus. Also, there is no significant correlation of bursting activity with extent of hearing loss. At the same time, the level of spontaneous activity significantly depends on the extent of hearing loss, though it is not related to the behavioral manifestation of tinnitus.

These results are consistent with our previous findings using salicylate-induced tinnitus and strongly support the postulate that bursting activity represents the tinnitus-related neuronal activity [3]. The observation that significant correlation occurs within the frequency range corresponding to maximal damage to the cochlea further supports this hypothesis.

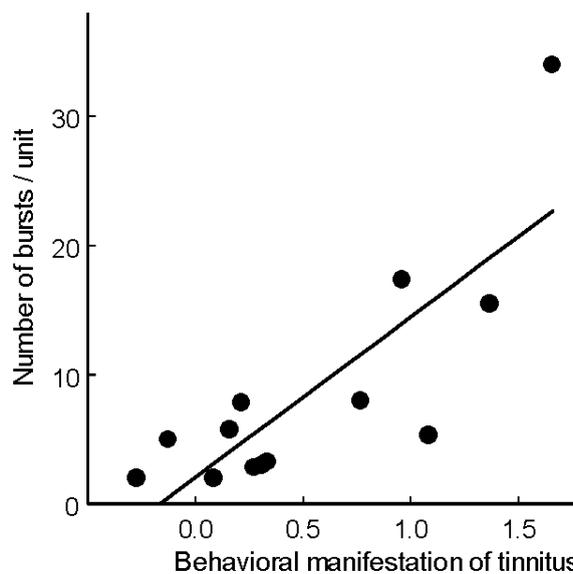


Figure 2 Correlation of the number of bursts recorded from units with characteristic frequencies between 5.5 and 15.5 kHz with the behavioral manifestation of tinnitus. Note highly significant relationship (13 rats, $p < 0.001$).

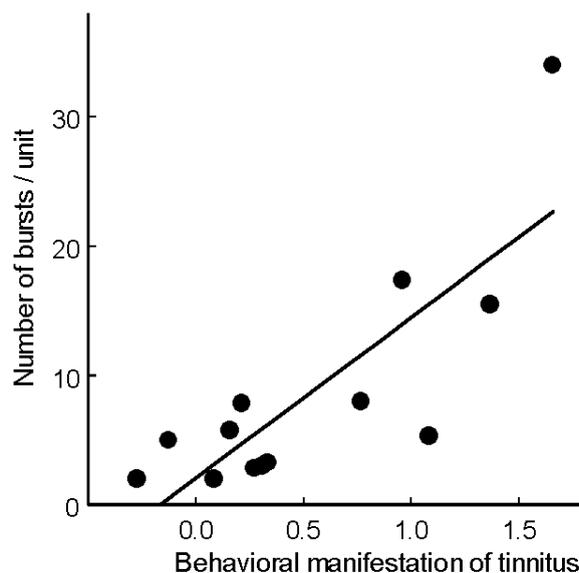


Figure 3 Correlation of the number of spikes in bursting activity recorded from the same units as in Fig 2 with the behavioral manifestation of tinnitus. Note highly significant relationship ($p < 0.001$).

The statistically significant dependence of the average rate of the spontaneous activity on hearing loss and the lack of significant correlations of the spontaneous activity with the behavioral manifestation of tinnitus are consistent with the postulate, that the increase of the spontaneous activity reflects adaptive changes within auditory neuronal pathways to hearing loss but is not directly related to tinnitus.

If the bursting type of activity, rather than the general increase of activity, is the neuronal correlate of tinnitus, it holds significant implication for

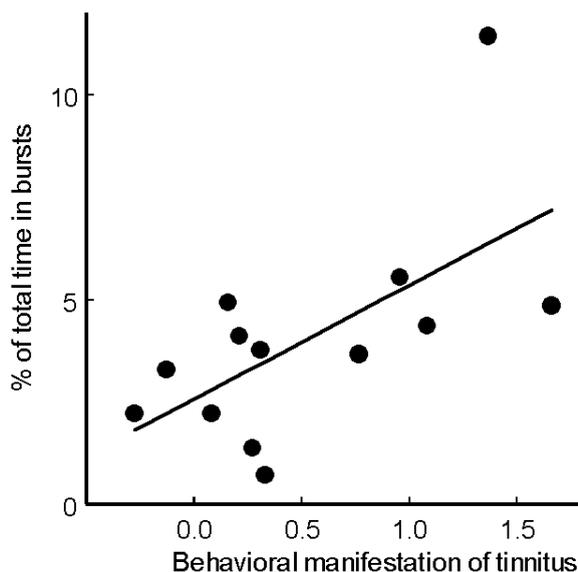


Figure 4 Correlation of the percentage of time of the bursting activity with the behavioral manifestation of tinnitus. Note highly significant relationship ($p < 0.05$).

studies using techniques aimed at evaluations of the changed in the metabolic activity of the brain (e.g., 2-deoxy glucose, PET, SPET, fMRI). These methods are not sensitive to changes in temporal patterns of activity, if they are not accompanied by a significant overall increase of neuronal activity. Since in our experiments the mean rate of spontaneous activity showed only a moderate increase in sound-exposed animals as compared to the controls, then it is unlikely that these methods would be helpful in detecting tinnitus-related bursting activity. Assumption that bursting activity is the neuronal correlate of tinnitus may explain the lack of modification in the metabolic activity in auditory pathways after salicylate administration or after noise overexposure reported recently.

However, methods aimed at evaluating changes in basic metabolic activity could detect a sustained change of activation in the limbic system, the presence of which is postulated in the neurophysiological model of tinnitus. Indeed, increased

activation of the limbic system in tinnitus patients have been reported with utilization of PET technique [8]. Work is in progress on detailed characterization of bursting activity and the correlation of its extent with specific patterns of damage of the cochlea.

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Case report: Tinnitus as first symptom of vasvular loop of anterior inferior cerebellar artery

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The association between vascular loops of the Internal Auditory Canal and symptoms suggestive of retrocochlear pathology (VII pain, VII palsy, hearing loss, tinnitus and vestibular disorders) has been described in several papers.

We present a case of a 69 year old woman with a history of tinnitus; Neurologic and audiometric test were normal. After a year, her tinnitus became worse and a new audiometric test revealed a mild right hearing loss. ABR showed a delay of I and II waves and a prolonged wave I–II interval. MR angiography revealed a vascular loop of the AICA within the region of the Internal Auditory Canal. We introduced her into our Retraining Therapy Program due to the absence of disabling symptoms to consider a decompressive surgery.

We discuss the importance of a careful diagnosis of this pathology as many times these findings raise a diagnostic dilemma with other retrocochlear lesions like acoustic neuromas.

Introduction

The association between vascular loops of the internal Auditory Canal and symptoms suggestive of retrocochlear pathology (VII cranial nerve pain, VII palsy, hearing loss, tinnitus and vestibular disorders) has been described in several papers. Many times these findings raise a diagnostic dilemma with other retrocochlear lesions like acoustic neuromas.

Material and methods

Case report: a 69 year old woman was seen initially with a 3-year history of tinnitus. The neurotologic and audiometric studies (tonal audiometry, ABR, caloric-rotational test) only revealed a moderate bilateral hearing loss in high frequencies and right labyrinth hyperreflectivity.

After a year without changes, the tinnitus got worse. A new audiometric test revealed a mild right hearing loss that involved conversational frequencies (Figure 1). Tinnitus was tested and psychoacoustic characteristics were: pitch (2000 Hz

narrow band noise), loudness (11 dB over threshold), minimal masking level (4 dB over threshold) and negative residual inhibition. Discomfort threshold level showed a mild hyperacusis on right ear. ABR showed a delayed of I and II waves and a prolonged wave I–II interval. Transient Evoked Otoacoustic Emissions (TEOAEs) and Distortion Product OAEs (DPOAEs) are shown. In view of these findings a MR angiography was performed reporting a vascular loop of the AICA (anterior inferior cerebellar artery) within the region of the internal Auditory Canal, with inflammatory changes in the ipsilateral VIII cranial nerve. A decompressive VIII PC surgery was evaluated but in the absence of disabling symptoms it was elected to observe the patient. Six months later, her auditory studies revealed unchanged threshold to her last results. Her tinnitus became worse and we introduced her into our Retraining Therapy Program (Directive counselling plus binaural white noise generators)

Discussion

Cadaver studies have documented intracanalicular extension of AICA in 40–67% of specimens. These findings are usual casual and in most of the cases,

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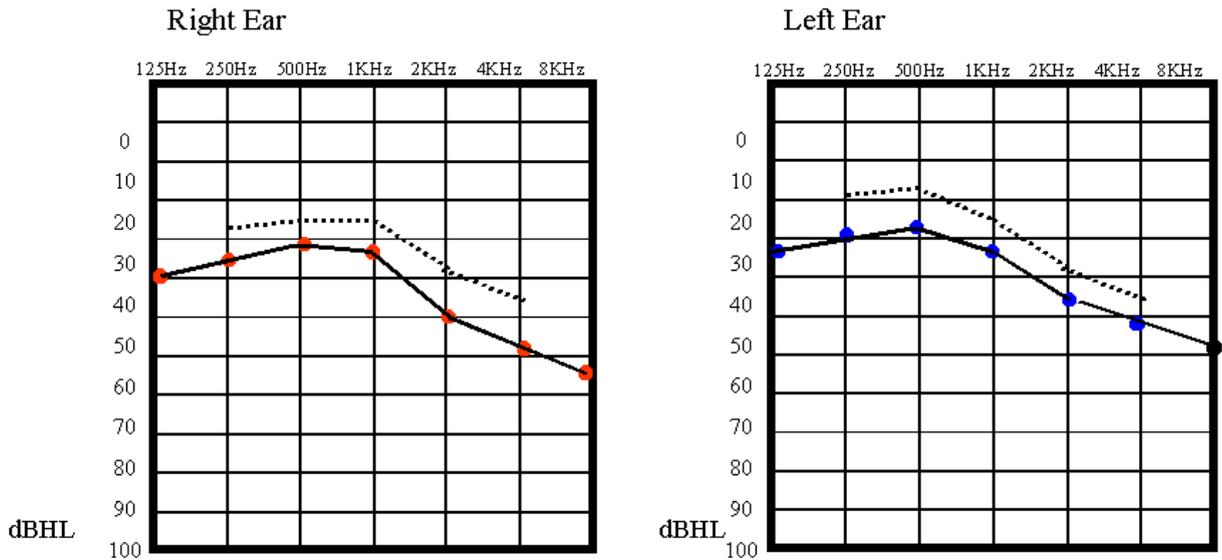


Figure 1

these individuals are asymptomatic. As a result, there has been generalized skepticism to accept the relation between symptoms and the compression of the neural structures (lower cranial nerves) secondary to these vascular loops. In the other side, there are authors that have found tinnitus, hearing loss and vestibular dysfunction as attributable to these malformation. We think that it is necessary to be careful with the diagnosis of these patients, not forgetting the possibility of this pathology, specially in those cases where a neoplasm is suspected.

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A neurophysiologically-based weekend workshop for tinnitus sufferers

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Intensive group therapy was performed with 40 participants. This blended temporary coping strategies with elements of neurophysiologically based tinnitus management. The four-month post-workshop measures indicated significant mean improvements in tinnitus distress, severity, and relaxation levels. The group format appeared to be beneficial for most participants, and enabled greater resource efficiencies compared with one-to-one counselling.

Introduction

New advances in the understanding of tinnitus pathoneurophysiology and rehabilitation have enabled a far more positive prognosis for sufferers. There is, however, very little empirical data available on the effectiveness of directive counselling when it is presented in an intensive group-workshop format. The group therapy-type approach has the potential to constitute an encouraging, peer-supported environment that might be more effective than one-to-one counselling.

Given that much of this information is common to all people with tinnitus, a group therapy approach might theoretically be able to reduce the inherent duplication of presenting this information individually in a clinical setting.

Wayner [1] described success with a weekend workshop for tinnitus using a cognitive therapy and relaxation exercise based approach, but did not publish any pre-post measures data that could be analysed statistically. However, the follow-up suggested that the initial gains were maintained 3 years afterward, and that relaxation training was voted to be the most beneficial aspect.

A prominent group of authors [2] has identified the need for research into establishing whether individual, group, or bibliotherapy-based approaches might be the most effective in reducing tinnitus distress. The present study will attempt to produce a group-therapy/workshop treatment partly based on Professor Jastreboff's neurophysiological model [3]. It will then be performed over an intensive weekend, and its outcomes longitudinally measured.

Methods

The workshop was conducted over two consecutive days in the capital city of Tasmania, an island state of Australia. Prior to the workshop, the two regional television stations for the evening news interviewed the author. A total of 253 enquires regarding the workshop were received by the host self-help group, but only the first 40 consecutive applicants were accepted (29 men, 11 women), in order to ensure that the workshop was a size that would allow sufficient interaction between participants (Ps).

Before beginning the workshop's educational sessions, two questionnaires were circulated to all Ps. The major instrument was the pre-therapy Tinnitus Reaction Questionnaire [4]. The other was a Tinnitus Beliefs Questionnaire, which was adapted from the negative tinnitus beliefs described by Hazell [5]. Both were dispensed with the suggestion that they can also help identify key tinnitus distress situations and specify negative beliefs about their tinnitus.

Each day of the program was divided into four 90 minute blocks, separated by rest breaks or lunch periods in which considerable liaison between the Ps occurred. Day One focused primarily on interactive-style lectures, including instruction on progressive muscle relaxation training. Day Two constituted the self-help portion, with Ps dividing into four groups of around ten each to discuss their individual experiences and plans for the future. To cater for the specific needs of the hearing impaired, detailed overhead projection summaries were used during the lecture-style sessions, and all Ps were given paper copies.

The central tenet of the workshop was that science's understanding of tinnitus has increased enormously in recent years, and that it is now recognised to be a disorder of central auditory processing,

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strongly enhanced by the limbic system. As a result there is now a considerable amount that can be done to reduce its immediate effects on sufferers' lifestyles, while also striving for the long-term retraining of their tinnitus perception. Some of the original ideas and strategies presented at the workshop were developed from the author's clinical experience and research activities. Other techniques were a synthesis of cognitive therapy, coping strategies, and also the latest neurophysiologically based theories [6]. The workshop used these in a layperson-oriented framework that attempted to demystify the experience of disturbing tinnitus. The need for appropriate acoustic stimulation was highly emphasised. Several forms of relaxation training were provided, combining progressive muscle relaxation practice with cognitive and time management strategies.

A deviation from conventional TRT was that coping strategies were advocated. The coping strategies were promoted as an interim measure to reduce the effects of tinnitus on their lifestyle, thus providing relief and control, and ultimately any limbic system enhancement of the tinnitus signal. Positive experiences of these coping strategies were shared between Ps over the course of the weekend.

The second day was much more interactive, often breaking into smaller groups for structured cohort interaction. There was also time allocated for private reflection on their personal beliefs/misbeliefs about tinnitus. One of the final items of the workshop was each individuals' completion of their own written Goals and Action Plan to consolidate the weekend's information and strategies. By consensus, Ps expressed their aversion to giving their initial Tinnitus Beliefs Questionnaires to the author, stating that after the weekend's information sessions, many of their negative beliefs had been successfully challenged and so the initial questionnaires were not reflective of their current attitudes.

Based on the technique of Coles [7], visual analogue scales were produced to obtain measures of

post-therapy Tinnitus Severity, Relaxation and Hyperacusis levels. These were pre-therapy anchored at 5, with an improvement towards 1, and a deterioration towards 10. They were posted to all Ps four months after the completion of the workshop. Tinnitus Reaction Questionnaires were also posted to those who had submitted one prior to the onset of the workshop programs' instruction activities. The 16-week period between the workshop and the post-therapy measures was incorporated to circumvent any short-lived benefits. It would also allow sufficient time for Ps to facilitate some of the suggested lifestyle changes and to become proficient at relaxation exercises.

Results

Of the 40 Ps, 34 returned their four month post-workshop evaluation measures. As indicated in Table 1, most Ps rated the workshop as either a 'great help' or a 'moderate help'. Four Ps rated the weekend as 'no help', while one participant assessed its effect as 'worse', indicating that the workshop format was not effective for everyone. Many Ps wrote that they took great comfort from the support and encouragement afforded by a group-therapy setting, and the sense that they were not alone in their experiences.

Tables 2 and 3 indicate that there were significant mean improvements in Ps ratings of tinnitus severity and general relaxation levels. Mean ratings of hyperacusis levels did not display any significant improvement. Additional post-workshop data was able to be collected on the twenty-one Ps who had elected to give their pre-workshop Tinnitus Reaction Questionnaire (TRQ) to the Audiologist during the weekend. These Ps were mailed a post-workshop TRQ, along with the universal measures. Eighteen (85.7%) of these Ps completed and returned both types of measures. There was a 14

Table 1 Distribution of responses to the question "Please assess the effect of the tinnitus workshop by ticking one of the five boxes below".

| Response | Distribution | | | | |
|----------|--------------|---------------|-------------|-----------|----------|
| | Great Help | Moderate Help | Slight Help | No Help | Worse |
| N | 10 (29.4%) | 12 (35.3%) | 7 (20.6%) | 4 (11.8%) | 1 (2.9%) |

Table 2 Tinnitus reaction questionnaire and visual analogue scale data

| | Group Data | | | Severity VAS | Relax VAS | Hyperacusis VAS |
|------------|------------|-------|----------|--------------|-----------|-----------------|
| | TRQ1 | TRQ2 | % Change | | | |
| Mean | 34.14 | 22.89 | 39.50 | 4.03 | 4.07 | 5.0 |
| Std. Dev. | 26.25 | 22.81 | 34.96 | 1.47 | 1.57 | 2.0 |
| Std. Error | 5.73 | 5.38 | 8.24 | 0.25 | 0.27 | 0.34 |
| Count | 21 | 18 | 14.29 | 34 | 34 | 34 |
| Median | 25.0 | 14.5 | 42.44 | 4.0 | 4.0 | 5.0 |

Note. Post-therapy severity, relaxation and hyperacusis were visual analogue scales that were pre-therapy anchored at 5, with an improvement towards 1, and a deterioration towards 10.

Table 3 Paired t-test Results for post-workshop tinnitus distress, tinnitus severity, general relaxation levels, and hyperacusis.

| Measure | Mean difference | DF | t-Value | P-Value |
|-----------------|-----------------|----|---------|---------|
| TRQ1, TRQ2 | 14.22 | 17 | 3.64 | 0.0020 |
| Severity VAS | 0.97 | 33 | 3.86 | 0.0005 |
| Relaxation VAS | 0.93 | 33 | 3.45 | 0.0016 |
| Hyperacusis VAS | 0.00 | 33 | 0.0 | |

point mean improvement, which were both statistically and clinically significant. Three Ps data indicated an increase in their tinnitus distress, whilst the other 15 Ps TRQs indicated a reduction. Significant habituation of tinnitus distress was defined as a reduction of greater than 30% in TRQ scores [8]. Seventy-two percent of TRQ respondents displayed post-workshop improvements of at least this magnitude.

Discussion and Conclusion

Overall, it was clear that most Ps benefited substantially from this type of group therapy. However, it was not possible to accurately quantify the type of strategies employed by each participant as a result of the workshop, or to adequately control for their pre-workshop level of TRT knowledge. An informal comparison with the individualised counselling performed at the author's clinic suggested that the workshop Ps improvements were less homogenous. However, the group format was clearly much more efficient in terms of clinician time. There is the possibility that a combination of individual counselling, plus group information-giving sessions, could be even more effective.

In summary, both the individual comments and the improvement in pre/post therapy measures suggested that the weekend workshop was able to provide a valuable contribution to the lives of those who suffer from tinnitus.

Acknowledgements: Heartfelt thanks are extended to Ms Carol McGhee, the Better Hearing Australia (Tasmanian Branch) Director of Services, who with the assistance of her committee, instigated, arranged and hosted the workshop.

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Implicit theories of patients with tinnitus and their influence on impairments and coping strategies

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This study investigated the contents and the structures of implicit theories of patients with chronic tinnitus and their influence on impairments and coping strategies. Fifty tinnitus patients (24 females, 26 males) were recruited from the Tinnitus Outpatient Clinic of the ENT-Department of the General Hospital of Salzburg, and from Austrian tinnitus self-support groups. Patients were evaluated using a semi-structured interview (ISK), the Tinnitus Questionnaire (TF), and the Trierer Scale for Coping (TSK).

It was shown that implicit theories were different regarding self-diagnosis, reported symptoms, and beliefs about aetiology. Additionally, this study revealed that implicit theories were interrelated with patients impairments and coping strategies. These patterns may be a significant consideration for professionals treating tinnitus.

Introduction

Tinnitus is widespread among clients consulting ENT practitioners or hearing clinics. The extent of impairments varies widely among patients. Many of them do not find tinnitus distressing, but other patients experience it as extremely disturbing and disruptive to everyday activities and are highly distressed by their noises.

When tinnitus cannot be cured by medical treatment, patients need professional support to cope with their symptoms. Inadequate coping strategies are seen as one of the main reasons that tinnitus becomes chronic and patients are unable to habituate.

In other studies of chronic diseases (e.g. schizophrenia, pain) it was found that implicit theories of an illness are very important, affecting the patients experiences and handling of different symptoms. This was supported by this study as well.

Methods

Implicit theories of tinnitus were evaluated using a semi-structured clinical interview (ISK) [1]. The ISK is a German language method (Instrument

for Subjective Illness Theories) for the assessment of implicit theories on various illness dimensions (diagnosis, symptoms, epidemiology, aetiology, course, coping, treatment).

Subjective impairments were measured with the German version of the Tinnitus Questionnaire (TQ) [2]. The questionnaire includes 52 items with 6 subscales; emotional distress, cognitive distress, intrusiveness, auditory perceptual difficulties, sleep disturbances, and somatic complaints.

Specific coping strategies were measured by the Trierer Scales for Coping (TSK) [3], a German instrument consisting of 37 items with 5 subscales; rumination (RU), social support (SS), cognitive defence (BA), information search (SI), religious beliefs (SR).

Data were analysed using Pearson-Chi²-two sample test and t-test for independent samples.

Results

In this study fifty patients suffering from chronic tinnitus participated (24 females, 26 males). The mean age was 51.70 years with a standard deviation of 15.76 (min. = 19; max. = 85), 10% of patients were single, 70% were married, 18% divorced, and 2% widowed. Patients were recruited from the Tinnitus Outpatient Clinic of the ENT-Department of the General Hospital of Salzburg and from Austrian tinnitus self-support groups during 1999. Patients

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had suffered from tinnitus for a mean duration of 7.13 years (min. = 0.50, max. = 43.00) with a standard deviation of 9.82. The patients' education level ranged from an elementary school to university graduate.

Patients, who labelled their noises as "tinnitus", reported more high pitch sounds ($\chi^2 = 4.69$; $df = 1$; $p < 0.05$), and acoustic symptoms ($\chi^2 = 5.89$; $df = 1$; $p < 0.05$) and believed more in

psychological causes of their illness ($\chi^2 = 6.46$; $df = 1$; $p < 0.05$). Patients, who didn't label their ear noises as tinnitus, described more often low pitch sounds, reported acoustic, as well as, other symptoms (e.g. hearing impairments, vertigo, headache, pain in the ears), and attributed their illness more often to organic causes. Additionally low pitch sounds were more often attributed to organic causes ($\chi^2 = 6.77$; $df = 1$; $p < 0.01$).

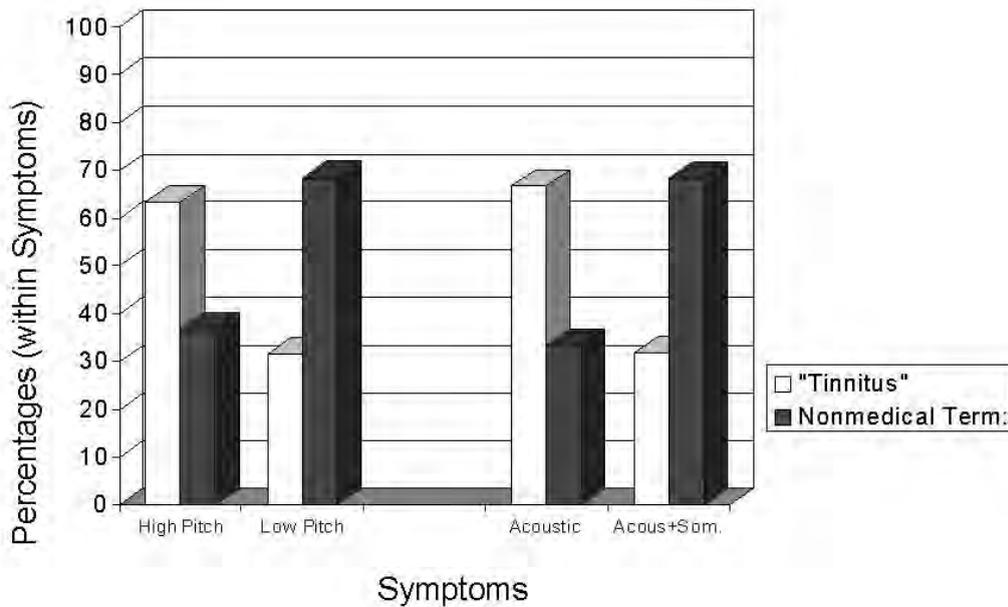


Figure 1 Relation Between Diagnosis ("Tinnitus"/Nonmedical Term) and Symptoms (High/Low Pitch; Acoustic/Acoustic + Somatic)

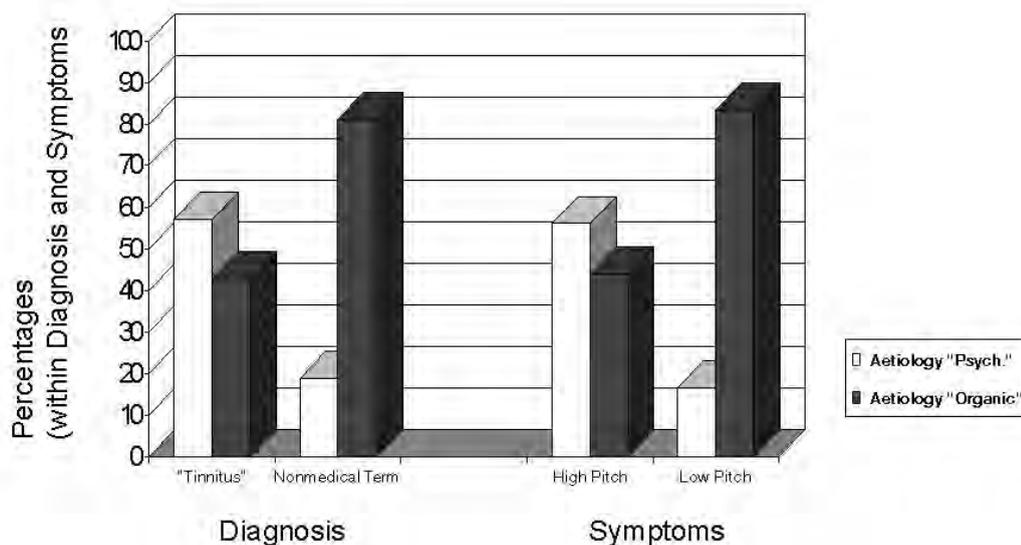


Figure 2 Relations Between Aetiology (Psychological/Organic), Diagnosis ("Tinnitus"/Nonmedical Term) and Symptoms (High/Low Pitch)

Table 1 Mean Values (mean) and Standard Deviation (sd) of different categories of implicit theories (Diagnosis, Aetiology, Symptoms) and dimensions of the coping scale (**Bold:** significant relationships).

| Categories of Implicit Theories | Tinnitus questionnaire (TF) | | | | | |
|---------------------------------|---------------------------------------|------------------------|--------------------------------------|---------------------------------------|--------------------------------------|--|
| | Emotional | Cognitive | Somatic | Intrusiveness | Hearing Impairments | Total |
| “Tinnitus” Diagnoses | mean: 9.48 sd: 5.00 | mean: 6.76 sd: 3.33 | mean: 1.60 sd: 1.85 | mean: 8.64 sd: 3.54 | mean: 3.80 sd: 3.50 | mean: 32.92 sd: 15.98 |
| Nonmedical Term | mean: 12.62 sd: 6.20 | mean: 9.50 sd: 4.43 | mean: 2.33 sd: 1.97 | mean: 10.46 sd: 3.98 | mean: 4.78 sd: 4.05 | mean: 43.17 sd: 18.83 |
| Internal Aetiology | mean: 10.00 sd: 5.26 | mean: 7.50 sd: 4.40 | mean: 0.78 sd: 0.89 | mean: 7.71 sd: 3.24 | mean: 3.21 sd: 3.51 | mean: 31.86 sd: 14.75 |
| External | mean: 11.48 sd: 6.19 | mean: 8.21 sd: 4.02 | mean: 2.41 sd: 1.99 | mean: 9.83 sd: 3.79 | mean: 4.31 sd: 3.65 | mean: 39.31 sd: 18.86 |
| Acoustic Symptoms | mean: 9.70 sd: 5.58 | mean: 7.45 sd: 3.85 | mean: 1.37 sd: 1.78 | mean: 8.89 sd: 4.01 | mean: 3.59 sd: 3.61 | mean: 34.04 sd: 17.45 |
| Acoustic + Somatic | mean: 12.83 sd: 5.69 | mean: 9.00 sd: 4.24 | mean: 2.56 sd: 1.93 | mean: 10.30 sd: 9.54 | mean: 5.39 sd: 3.86 | mean: 43.00 sd: 38.16 |

Further, patients labelling their ear noises as “tinnitus” experienced less impairments, especially in the dimensions of emotional distress ($t = 1.95$; $p < 0.05$), cognitive distress ($t = 2.44$; $p < 0.01$), and intrusiveness ($t = 1.69$, $p < 0.05$), than patients who didn’t regard their ear ringing as tinnitus.

Patients who believed in external causes of their illness (e.g. work problems, accident, din) complained significantly more about somatic impairments due to tinnitus ($t = 3.78$; $p < 0.01$), experienced their noises as more intrusive ($t = 1.69$; $p < 0.05$) than patients who attributed their illness more to internal causes (e.g. rumination, stress, dissatisfaction). But they did not experience more impairments all in all. Moreover, patients who

described other symptoms in addition to acoustics symptoms (e.g. vertigo, headache, pain in the ears), were more emotionally distressed ($t = 1.95$; $p < 0.05$), as well as, somatically impaired ($t = 2.27$; $p < 0.05$), they more often reported hearing impairments than people who only described acoustic symptoms ($t = 1.69$; $p < 0.05$) and they were entirely more impaired too.

Additionally the analysis showed, that patients who labelled their ear noises as “tinnitus” ($t = 1.68$; $p < 0.05$), who attributed their illness to external causes ($t = 1.99$, $p < 0.05$), and who experienced only acoustic symptoms ($t = 1.68$; $p < 0.05$), used social coping strategies more often than patients who described their ringing in nonmedical terms,

Table 2 Mean Values (mean) and Standard Deviation (sd) of different categories of implicit theories (Diagnosis, Aetiology, Symptoms) and dimensions of the tinnitus questionnaire (**Bold:** significant relationships).

| Categories of Implicit Theories | Trierer Scale of Coping (TF) | | | | |
|---------------------------------|------------------------------|---------------------------------------|-------------------------|-------------------------|------------------------|
| | RU | SS | BA | SI | SR |
| “Tinnitus” Diagnoses | mean: 28.40 sd: 8.30 | mean: 34.24 sd: 8.45 | mean: 35.32 sd: 6.14 | mean: 26.52 sd: 7.41 | mean: 7.04 sd: 3.77 |
| Nonmedical Term | mean: 29.37 sd: 8.73 | mean: 30.21 sd: 8.31 | mean: 33.54 sd: 5.07 | mean: 23.92 sd: 8.40 | mean: 7.62 sd: 4.06 |
| Internal Aetiology | mean: 28.43 sd: 7.90 | mean: 28.00 sd: 8.70 | mean: 33.57 sd: 6.09 | mean: 22.43 sd: 9.27 | mean: 6.43 sd: 4.41 |
| External | mean: 29.90 sd: 8.44 | mean: 33.52 sd: 8.01 | mean: 34.07 sd: 5.12 | mean: 25.83 sd: 7.80 | mean: 7.90 sd: 3.56 |
| Acoustic Symptoms | mean: 28.41 sd: 8.60 | mean: 34.00 sd: 7.18 | mean: 35.22 sd: 5.06 | mean: 24.89 sd: 7.71 | mean: 6.93 sd: 3.78 |
| Acoustic + Somatic | mean: 29.74 sd: 8.31 | mean: 29.91 sd: 9.55 | mean: 33.30 sd: 6.21 | mean: 25.13 sd: 8.58 | mean: 7.61 sd: 4.07 |

who believed in internal causes, and who reported different somatic symptoms in addition to the acoustic symptoms.

Discussion and conclusion

In our study we found two types of tinnitus sufferers:

The first group labelling their ear ringing as "tinnitus" experienced more often high pitch sounds and reported fewer additional somatic symptoms. They attributed their illness more often to psychological causes and were less impaired, especially emotionally and cognitively. They experienced their noises as less intrusive and were seeking social support and social activities as a mean of coping with tinnitus at higher rates.

The second group used a nonmedical term to describe their acoustic sensations, reported more often low pitch sounds, and were more impaired, especially in their emotions and cognitions. They experienced their noises more intrusive and tended to believe in somatic causes of their illness.

This study revealed that different aspects of implicit theories are interrelated with patients impairments and coping strategies. These results may be of significant importance for professionals treating tinnitus and they suggest, that the development of specific strategies for systematic modification of implicit theories of tinnitus will lead to an increased efficacy of treatment and compliance, and an improved illness behaviour and coping.

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A new tinnitus-counselling tool: Tinnitus perception explained by “BoE” (Barometer of Emotion)

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The experience acquired in the ongoing tinnitus study in Bad Meinber, Germany, shows clearly that intensive patient counselling must take place before any therapy is started. This puts the patient in a position to understand their symptom, and they can thus develop a tool for managing their ear noise by interrupting the feedback-loop of self-generation of emotion and attention.

Bearing in mind that the loudness of the tinnitus never exceeds a volume of just a few dB it seems incredible that such a low-level noise sometimes penetrates the tinnitus patient like an aircraft taking off.

BoE is an absolutely new way of explaining to the patient just how the tinnitus noise can attain such an unbearable loudness. During this running study, more than one thousand tinnitus patients were instructed about this phenomenon in lectures and counselling sessions taking the BoE graphic on the heartbeat in a sound-proof chamber as an example. Tinnitus is generated in the same way as the heartbeat explained in this BoE graphic. The patient will thus learn to readily understand the principle of “self-generated audible body sounds”.

This BoE graphic finally makes it possible to set up the various ways of therapy on an individual basis to suit the requirements of the tinnitus patient. The fact that the patient themselves understands the complexity of the symptom “tinnitus” much better means that the therapy in the follow-up is significantly more effective through improved self-management.

Method

“How” to explain the phenomenon of “tinnitus” to people?

According to the experience acquired in almost one hundred information lectures to approx. 3000 people and also during individual counselling sessions with more than one thousand patients, it is very important to find the right words and appropriate tools to explain such a complex phenomenon as tinnitus.

Working on the basis of the “transactional stress model” (1) BoE has been developed to provide such a tinnitus-counselling tool for the initial information of persons affected by tinnitus. The effective presentation of BoE, supported by self-explanatory PC-animated illustrations, will help to make this symptom understandable to everybody, i.e. to people who are not generally educated in physiological matters.

The tinnitus-information lecture generally starts with a basic explanation of the function of the ear, with special focus on the inner ear, trying to give hypothetical answers to the questions of “where and

how” the tinnitus noise is generated initially before it becomes established in the brain. Once it has manifested itself in the additional brain, it is important to understand that the loudness of the noise is controlled by the person affected through various emotional feedback-loops.

BoE consists of six parameters, initiated by *perception* which is either lacking or highly intensive. The value for perception will influence the *emotional reaction*, which initiates the effect on the *first* and *second appraisal*. The *final appraisal* then controls *attention*, which influences perception once again. This system generates three feedback-loops between emotion, attention and perception.

The principle of BoE can be used for most emotional reactions. As the heartbeat, in particular, can be readily duplicated by everybody, we have decided to focus on the heart noise alone for explaining the phenomenon of rising attention and perception. Due to the three feedback-loops illustrated by BoE, even the heart noise can be magnified to giant dimensions and can lead to panic situations (see Figure 1).

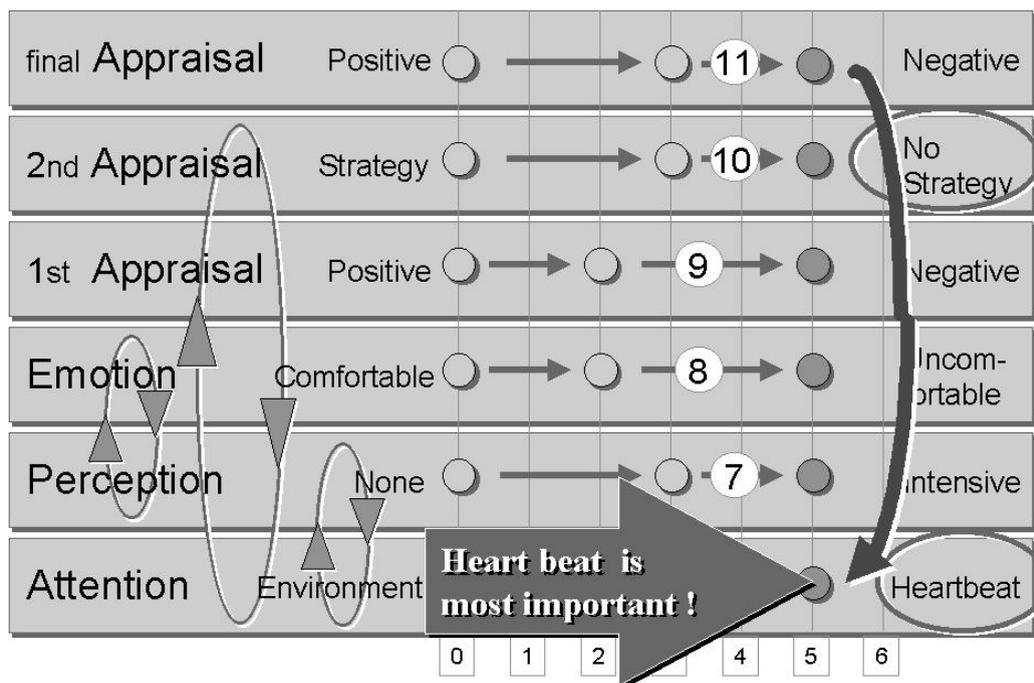


Figure 1 Heartbeat perception in a silence chamber

The function of this system can also be transferred to tinnitus noise, which will be generated by the feedback-loops in the same way as the heart noise. Thus the tinnitus patient starts to understand the correlation between attention, perception and emotional effects, which they themselves control. The more attention they focus on their tinnitus noise the more intensive their perception of this noise becomes.

Figure 2 shows the various steps of a successful tinnitus therapy based on the BoE model. The demonstration of the logical correlation between the three feedback-loops and the appropriate therapy based on the parameters of BoE is easily understood by everyone. This understanding forms the most promising basis for a successful tinnitus therapy (see Figure 2).

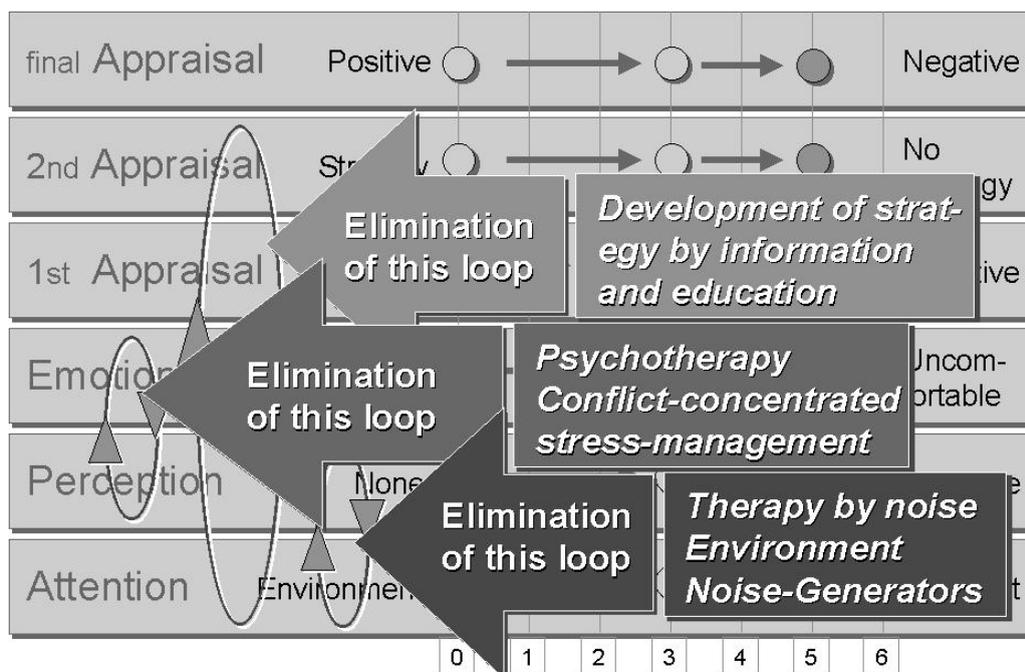


Figure 2 Tinnitus Therapy based on BoE

Results

Using BoE as a means of explanation has shown that people start to easily understand the complexity of the tinnitus noise generated in their brain. They also understand the correlation between perception, emotional reaction and attention and see that the tinnitus level is ultimately controlled by themselves.

Due to the better understanding of the symptom of "tinnitus", the therapy in the follow-up has a significantly better effect thanks to improved self-management.

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Tinnitus from a psychosocial perspective

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In patients (ptts) with severe annoyance due to tinnitus (T) crises, stress and other emotional states are highly prevalent. In our T programme ptts are approached within an existential and cognitive frame of reference and the comprehension of T and its individual consequences in a psychosocial context is considered essential. Thus the purpose of this contribution is to identify and describe psychosocial characteristics of a clinical group with severe T distress and to relate these data to comparative data from the background population whenever possible.

Introduction

Material

Totally = 407 ptts (median age 49 years, range 9–93, 57% males, 43% females) with severe T annoyance, who during a two years period have been treated in our programme including sessions with a clinical psychologist (median two sessions, range 1–10). Ptts are highly selected (according to the questionnaire of Coles *et al.* 1992 [1]) as those, who experience a large impact from T upon everyday life. 35% had hearing within normal range (BEHL 0.5–4 kHz < 20 dB HL) and additionally 22% had hyperacusis. Only 11% had no instrumental trials, while the remaining were fitted with maskers (63%), HAs (18%), masker and HAs (8%). For the purpose of the study the material was divided into four subgroups according to employment status as defined in The Statistical Yearbook of Copenhagen 1998 [2]: Group 1 = still employed (N = 192, 47%), Group 2 = students (N = 58, 14%), Group 3 = unemployed, early retirement pensioners and individuals receiving assistance under the Social Assistance Act (N = 90, 22%) and Group 4 = old age retirement pensioners >65 years (N = 48, 12%), unknown = 19, 5%). In Group 3–4 no ptts are unemployed or have retired primarily due to T. The material is representative by distribution according to local city districts. An overrepresentation of men is found as compared to the background population (see also results), whereas immigrants are underrepresented.

Methods

A retrospective case study. Following each psychological session extensive information was entered

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into the ptts case sheet. Relevant data were extracted and stored into a database together with results of the oto-audiological examinations. For the present purpose focus is upon data from the subgroups according to employment status and incidence of somatic diseases moderate/severe (of all kinds), psychic disturbances (depression, anxiety, life crisis) and psychosomatic disturbances (sleep disturbances, stress, pain and concentration) as compared to the background population (Danish National Board of Health, 1997 [3]). For statistical purposes Confidence Limits were applied (P = 0.05).

Results

Employment status

Among T ptts a significant higher proportion are unemployed, early retirement pensioners or individuals receiving assistance under the Social Assistance Act, and a significant lower proportion are old age retirement pensioners as compared to the background population. Furthermore ptts with severe T distress differs from the background population in the sense that a significant higher proportion are men in the groups of employed (N = 119/192, 62%), unemployed, early retirement pensioners and persons receiving assistance under the Social Assistance Act (N = 50/90, 56%) and students (N = 33/58, 57%).

Somatic diseases

In the age group 15–64 years T ptts have a higher somatic morbidity (males/females 43%) as compared to the background population (males 20% and females 33%). Compared to their representation in the material women have higher somatic

morbidity as compared to men, which tendency is also found in the background population. The proportion of somatic diseases in the four subgroups according to employment status is: Group 1, N = 70 (37%), Group 2, N = 12 (21%), Group 3, N = 51 (57%) and Group 4, N = 25 (52%). Group 3 (unemployed etc.) have a significant higher proportion of somatic diseases as compared to the other groups.

Psychic disturbances

In the total material N = 96 (24%) suffers from psychic disturbances. For comparison with a background population the only available data is the number of discharges from hospitals (in- and out-ptts), which is N = 91,326/5,500,000 (total population in DK) (2%). In the subgroups according to employment status the proportions of psychic disturbances are: Group 1, N = 37, 19%, Group 2, N = 7, 12%, Group 3, N = 31, 36% and Group 4, N = 19, 40%. Thus a significant higher proportion of psychic disturbances was found among T ptts not associated with the employment market as compared to still employed and students.

Psychosomatic disturbances

Totally N = 247 (61%) have one or more psychosomatic disturbances. No data is available for comparison with the background population, but the number is expectedly high, as the symptoms are those normally encountered in T ptts. Ptts still employed most often suffers from stress (N = 64, 53%), whereas students most often experience problems with concentration and stress (N = 33, 89%). Ptts, who are unemployed, early retirement pensioners or individuals receiving assistance

under the Social Assistance Act most often suffer from pain (N = 20, 32%) and old age retirement pensioners state sleeping problems as a major psychosomatic disturbance (N = 7, 33%).

Conclusion

The study shows that in a group of highly selected ptts with severe distress due to T a significantly higher proportion is marginalised in the sense that they are without connection to the labour market as compared to the background population. Furthermore severely distressed T ptts have a higher morbidity as compared to the background population – remembering that ptts are not unemployed, early retirement pensioners or individuals receiving assistance on the Social Assistance Act primarily due to T. Finally the socially marginalised T ptts in the study have a significantly higher morbidity than T ptts who are still employed or students. The study shows the importance of including the psychosocial context in the understanding of the psychodynamics of T, the individual coping ability and thus the treatment of T ptts.

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The Swiss concept II: Holistic body work

Zogg R

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The Swiss holistic rehabilitation concept [1] includes measures improving the general well-being of the patient. Psychotherapy, measures restoring the sleep disorder and antidepressive treatment are recommended according the individual needs. Additional body work was found to improve the rehabilitation results significantly. Tinnitus counselling is directed to the intellectual reasoning and tends to neglect the fact, that tinnitus is a somatic symptom. Holistic body work bridges psychotherapy and somatic tinnitus reactions. Tinnitus leads to various body reactions which mix with preexisting (and often inveterated) protective body reactions. Body work can unwind the past history, as it is concealed in the body e.g. in frozen muscle contractions. Such frozen contractions cannot be resolved by simple relaxation techniques such as autogenous training. Body work methods are process inducing and integrative such as Feldenkrais [2], sensory awareness (Selver and Brooks [3]), Atemtherapie (Middendorf), eutony (G Alexander [4]), postural integration (Painter), somato-emotional release (Upledger).

Awareness of the body and increasing comprehension of its messages induce a process that involves somatic symptoms as well as psychological blockades. This process slowly removes hindrances which tend to interfere with tinnitus coping as it is aimed at by TRT. Scarcely a tinnitus patient lacks significant problems beside the tinnitus. A holistic approach is a demanding task for the patient as well as for the therapist. A holistic evolutionary process, however, leads to proper understanding of the various problems on the biological, somatic and social level. The various problems are put in an appropriate order of their priority – and tinnitus often winds up as a problem of minor importance. The final goal is a coping ability which by far exceeds the ability to cope with tinnitus.

Body work methods and psychotherapy

Somatic medicine and psychotherapy tend to divide their working fields into somatic and psychological problems. The gap between those fields, however, does not match with our own holistic experience of ourselves. On the one hand, psychosomatic medicine aims at bridging the artificial gap. On the other hand there are body work methods, which try to use the interactions between psyche and body for therapeutical purposes. Unlike physiotherapy, these methods do not confine themselves to restoring impaired body functions. They also differ from relaxation techniques with their restricted goal of lessening psychological and somatic tensions – thus improving the momentary well being. Body work methods try to induce a long lasting process on the psychological level as well as on the level of the body. Unfortunately, these methods did not yet find the general acceptance which they deserve. They do not construct new holistic theories, but they use

self-experience and body awareness as their main principles.

Body work methods cannot be learned from books – they need years of learning under the personal supervision of an experienced teacher. Their effect is felt, but it cannot be measured easily. Therefore body work methods lack sufficient scientific recognition. Wrongly they are often lumped together with obscure healing procedures beyond the classical medicine.

Body work methods in tinnitus rehabilitation

Tinnitus can lead to a severe crisis on both the somatic and the psychological levels. Improvement in such cases does not necessarily comprise a disappearance of the tinnitus. True tinnitus rehabilitation means a holistic process which includes problems not directly related to tinnitus. The crisis has to be overcome, and the individual gets more strength for further new strains. The tinnitus may remain, but it has found its proper place in the individual's life. Body work methods

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are better suited for inducing such an evolution than pure psychotherapy. After proper counselling, many tinnitus sufferers easily learn to accept their tinnitus on the mental level – but they do not improve because tinnitus remains an intrusion that cannot be controlled by mental strength. Body work methods try to integrate tinnitus in a holistic way, beyond the purely mental counselling. During body work therapy, the tinnitus sufferer soon forgets to repeat his or her tinnitus complaints. Other problems have regained their proper priorities. The patient does not continue the desperate search for tinnitus cure, but he or she regains the self-esteem, he or she had lost. The patient thus is better prepared for coping with tinnitus, and the retraining process is facilitated. According to our experience in tinnitus rehabilitation, body work increases the rate of significant improvements by approximately 10%. Prerequisites for a successful body work are: (a) the

patient's willingness to change, (b) proper schooling of the awareness and (c) a competent therapist.

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Tinnitus therapy in Germany

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Since 1995, when Tinnitus Retraining Therapy (TRT) was first introduced in Portland by Pawel Jastreboff, great enthusiasm began in Germany concerning the new aspects in treating tinnitus patients. Especially the direct management of the patient with counselling and sound therapy, brought a new motivation to transfer TRT into the German health system. In Germany, ENTs, psychologist, and acousticians felt responsible for Jastreboff's and Hazell's concept. ENTs for somatic diagnosis and somatic treatment, psychologists for psychological diagnosis and psychological therapy, and acousticians for the support of the patient with hearing aids and noise generators. The task for these professionals is to form a team around the tinnitus patient and to define the job and role of each member of this team. The goal was also to have TRT paid by the health insurance. Soon discussions began about the content of "German TRT", which obviously is different in some details compared to Jastreboff's original TRT.

Daily experience with Jastreboff's TRT showed a lack of psychological diagnosis and treatment especially for patients with severe tinnitus. Treatment in Germany began to include psychological care in the TRT concept. Similar considerations led to the development of the English term Neurophysiologically Based Management (NBM).

Finally, after reflecting on these issues, a new model of management strategy for treatment of tinnitus patients in Germany has been developed, and is explained by the poster.

Due to our strongly organised health system and due to the fact that the Anglo-American audiologist do not exist in Germany, the first step of a tinnitus patient will be the consulting of an ENT specialist. After audiological and somatic diagnosis and potential medical treatment in case of acute or specially defined tinnitus, the ENT-specialist indicates the further measures according to the complexity of the case and patient's claims. Using the following grad-

ing scale, based on clinical testing and observation, a treatment concept can be implemented.

Grade 1: Tinnitus is not disturbing.

Grade 2: Tinnitus is annoying in silence, amplification of tinnitus in "stress".

Grade 3: Tinnitus leads to different psychological disturbances and reduced quality of life; acoustic focusing all day. Tinnitus provokes private and professional problems.

Grade 4: Tinnitus makes a normal life impossible. Patient is no longer able to work, obviously psychological and/or psychiatric disorders combined with tinnitus.

The therapeutic considerations from this grading scale are the following:

Grade 1: No therapy, perhaps counselling.

Grade 2: Counselling, perhaps sound therapy (= TRT!).

Grade 3: Psychological diagnosis of tinnitus related psychological impairments, and other psychological problems/disorders. Depending on the results of diagnosis:

- No psychological treatment, perhaps TRT or
- Psychological treatment of the comorbidity (e.g. depression, anxiety), perhaps combined with TRT or
- Psychologically orientated habituation-training

Grade 4: Psychological diagnosis and treatment in tinnitus hospitals, followed by management strategies for grade 3.

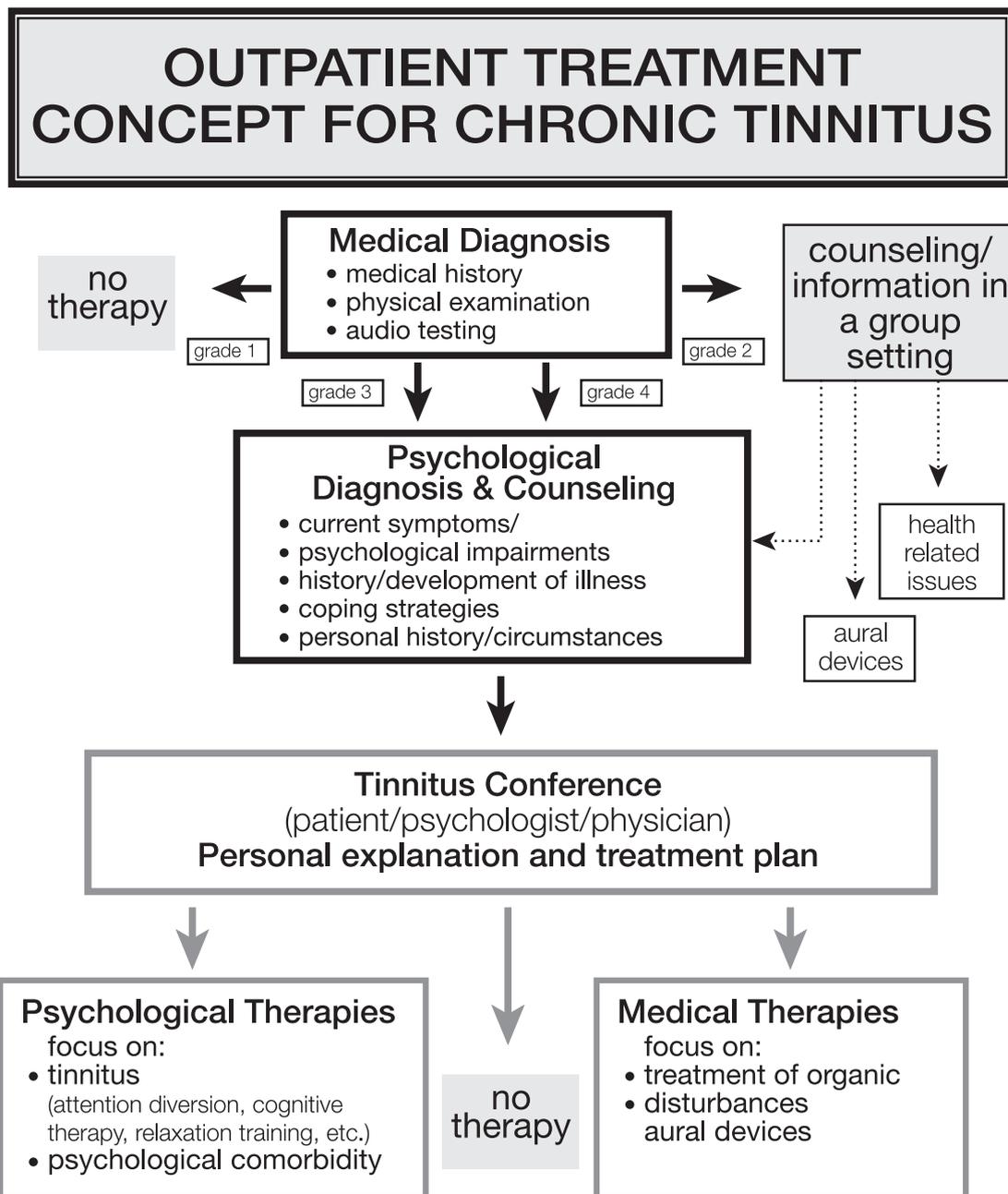
In this model, TRT takes place for lighter cases with no severe psychological problems. More severe cases have their clearly defined management strategy of diagnosis and therapy. The German model of tinnitus therapy also provides a definition for the teamwork of the professionals. It is strongly recommended, that there is a therapeutic team for the patient, to answer his/her questions, discuss sorrows and give support. The team

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consist of an ENT-specialist for the medical care, and a psychologist for the psychological disorders and complications, and when required an acoustician for the technical support. It must be stressed, that the teamwork includes common counselling of the team members together with the patient. Especially after the psychological diagnosis of tinnitus, a conference including the patient, psychologist, and ENT is necessary to discuss the individual's beliefs, and medical and psychological

problems. The therapeutic consequences from such a conference are more effective than individual counselling between the patient and each professional.

Finally, the German model of tinnitus management strategies, introduced by Jastreboff's TRT and adapted to the German health system, has received great acceptance by the authorities, but nevertheless, payment by the health insurance is not yet approved.



Clinical grading

Grade 1: Tinnitus is not disturbing

Grade 2: Tinnitus is annoying in silence, amplification of tinnitus in "stress"

Grade 3: Tinnitus leads to different psychological disturbances and reduced quality of life; acoustic focusing all day. Tinnitus provokes private and professional problems

Grade 4: Tinnitus makes a normal life impossible. Patient is no longer able to work, obviously psychological and/or psychiatric disorders combined with tinnitus

Living with hyperacusis: The world of constant noise

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The script was motivated by a hyperacusis patient† who collaborated with a professional recording studio to re-create the sound and feeling of her hyperacusis and tinnitus. To demonstrate the effect of this debilitating and mysterious affliction, Danny Scott, the studio owner, authored and produced a day in the life of two people: Sally who does not suffer from hyperacusis or tinnitus and Mike who does.

Introduction

A seven minute cassette tape to be used for educational and supportive purposes when accompanied by positive counseling and information including treatment possibilities and current research.

Results

- (1) Audiologists, physicians and related health care professionals will be more involved in hyperacusis/ tinnitus treatment and referral when they understand how patients with severe hyperacusis and/or tinnitus are affected.
- (2) Funding sources will be encouraged to provide money for tinnitus research when they understand the impact that hyperacusis and tinnitus have on people's lives
- (3) Hyperacusis/tinnitus patients will feel their therapy is based on the understanding the clinician has of the impact hyperacusis and or tinnitus has on their life styles.
- (4) Families of hyperacusis/tinnitus patients will have an understanding of the difficulties their loved ones encounter and will be encouraged to be patient as treatment is begun and improvement is evident, but not immediate.
- (5) (Second side, Sounds of Tinnitus) Lectures on tinnitus will be more effective when the listeners can hear similar sounds that a tinnitus sufferer experiences.

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†She has now recovered after 1 year using Tinnitus Retraining Therapy (TRT) and continues to advocate for the hyperacusis/ tinnitus sufferer.

- (6) Tinnitus sufferers will feel their tinnitus is objectified and, therefore, may be more effectively treated.

Discussion and conclusion

In the next few minutes we would like to show you how the world sounds to someone suffering from tinnitus – more specifically, tinnitus with hyperacusis. Tinnitus taken from the very innocent sounding Latin term for tinkling bell is anything but innocent. It is a severe and burdensome affliction that at its best robs its victims of much needed peace and quiet. And at its most severe end can simply drive the sufferer mad. Tinnitus is the constant presence of noise on one's ears. It is a never ending whistle, a buzz, a hum, a hiss, a maniacal one-noted flutist who never takes a breath. Typically it is a combination of two or more of these aggravating sounds in a constant concert of torture. Tinnitus with hyperacusis takes this condition to the next level of torment. This condition not only presents the symptoms just mentioned, but makes even the slightest noise sound like thunder. We would like to demonstrate what ordinary living sounds like to you or me.

Let's call our average person, Sally and we will call our tinnitus sufferer, Mike. In order to truly appreciate the misery Mike lives through 24 hours a day, try to imagine not being able to turn off the tape player. By now you are aware of a low level noise present on the tape. Irritating, isn't it?

Let's turn it off and give Sally a few moments to gather her thoughts before the morning alarm clock rings and she starts her day (*birds chirping and ringing alarm clock*). She showers, gets herself together and goes to the garage to get in her car and drive to work (*garage door opening, sound of the car starting, then the closing of the garage door and noisy traffic*). In

traffic she decides a little quiet music will take her mind off the bumper to bumper snarl and she's on her way.

Let's check on Mike and hear how his day sounds. He, too, has just awakened before the alarm clock, but the sounds of distant birds are already dominated by "the sound". Not that he's slept much but he is sure he is awake now in the presence of his every faithful companion, "the sound". He sees the alarm clock – 6:59. It hits him, "Can I get to it before it goes off?" (*alarm starts ringing*). Too late. Mike hasn't even left the bedroom and he sits back down to try to compose himself and block out the chaos in his head. That electric razor is going to sound like a buzz saw. He shaves with a blade and goes down to the garage. Mike waits a moment before he hits the garage door button. But he can't drive through the door, so . . . (*garage door opening, car starting, and the garage door closing*). At this point traffic is simply overwhelming with every engine and horn like a knife in his head. Playing music would just mean adding another noise to the dim that is his mind. And the day hasn't even started (*traffic noise*).

Sally's got a couple of chores to perform before work. There are some things she needs to pick up at the mall (*background music, people talking, etc.*). She needs to have her tires rotated (*auto repair noise*). And now she's at work in her office downtown. It's a beautiful spring day, so she opens her window for the fresh air (*traffic noise and people*).

As you guessed, Mike has the same errands to run, but Mike's journey through the mall is more like a mine field (*people talking, music*). He now re-thinks his tire situation but he has put it off too long and it must be done (*auto repair noise*). This is far too much for him; outside it has to be better. Sure enough, outside is where he hears the traffic, so he just endures. He's on his way now to his office downtown. Will he find refuge there with the phones, filing cabinets, loud conversation, copy machines and everything else? No, there is no refuge there or anyplace else. The first thing he has to do is ask Sally to close the window.

Such is the life of one who suffers from the debilitating and mysterious affliction known as hyperacusis and tinnitus. The purpose of this presentation is to educate and try to impart to those of us who can hear the silence what it is like for those who no longer can.

Second side – tinnitus sounds

Although there are a small group of common noises associated with tinnitus, it appears that there are as many variations of these noises as there are sufferers, each individual to the person. We would never be able to catalog *all* the sounds, but let's review the basic ones.

Describing sounds with words is always difficult. One person's ocean-like sound is another person's wind noise. You may hear a distant roar while the person next to you hears a quiet rumble. That is

why a tape like this can help so much with communication – a way to "get everyone on the same page" so to speak.

At the core of many tinnitus sounds is the whistle or pure tone. It varies in pitch for each individual but most often it is very high frequency. This sound also serves to prove that verbal descriptions are practically useless because most people would refer to this sound as a whistle, but in the vocabulary of tinnitus, it is called "ringing tinnitus".

Now this sound by itself is one thing, but often it has a companion tones. Two tones together can be musical – if they are complimentary tones. As harmonious as they may be, they are still uninvited sounds in one's head and are very, very rarely in harmony. The norm for two simultaneous tones usually create a dissonant noise.

The next most common sound is what is technically called white noise. Ironically, white noise generators are used to mask sound in noisy environments; however, hearing white noise outside one's head is quite different than hearing it *inside* one's head. Still many of the tinnitus devices generate this sound and effectively relieve some of the other noises tinnitus sufferers endure.

Like the ringing or whistle tone, white noise has variations also – quite a few, in fact. In the very low ranges it can sound more like a rumble or a distant helicopter. It can pulse in and out and sound something like the ocean. It can also sound like TV or radio static. Again there are as many different incarnations as there are people afflicted.

There are more exotic sounds that are common; but, from a sound engineer's perspective, they are simply variations of the ones we have already heard. There are sounds such as a whistling teapot sound, a field of crickets, and a fog horn. There are also combination sounds.

The white noise and the whistle or ringing sound are frequently together. Often the low rumble is accompanied by the teapot sound. Unfortunately the combinations are endless which makes this condition that much more frustrating. Our goal with this portion of the cassette is to help you identify and name some of the more common noises and thereby help you communicate what you hear.

Conclusion

The World of Constant Noise and Sounds of Tinnitus must be used with great care for patients with hyperacusis and tinnitus. They should only be heard in a counseling context to demonstrate that the clinician understands the problem the sufferer is experiencing and validate the stress the patient is feeling. The tape must be embedded in a session explaining there are treatments which will alleviate this situation. The tape will be even more valuable for physicians, audiologists and other health-care professionals to understand the impact hyperacusis and tinnitus have on the life styles of those who suffer. Hopefully, this will lead to better patient care, advocacy and research.

Tinnitus retraining therapy: Our experience

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First described by Jastreboff and Hazell in 1990–93, TRT is today, one of the most successful treatments for tinnitus habituation. We present a study of 172 patients included in our TRT program. We have used directive counselling (DC) alone in 37% of the cases, DC plus hearing aids in 46% and DC plus white noise generators in 37%. Results are evaluated at one year follow-up period. Patients consider TRT as an effective approach for tinnitus habituation according to their own subjective evaluation (88% of the cases). Handicap questionnaires and analogical measurement scales on tinnitus intensity did not show a considerable improvement in this series (47.6% according to tinnitus handicap inventory and 32.1% in visual analogical scales).

Introduction

Since 1990, tinnitus management approach by retraining therapy (TRT) has involved many otolaryngologists and audiologists around the world. Described and first applied by P Jastreboff [1,2] in Baltimore, USA and J Hazell [2] in London, UK, TRT is today, one of the most successful treatments for tinnitus habituation.

We started using this approach in 1996. Our protocol includes an exhaustive otolaryngological history, a complete cochleo-vestibular battery test, complementary explorations, tinnitus data, patient's subjective evaluation of the tinnitus (visual analogical scale, annoyance scale, tinnitus handicap inventory – THI [3]) and psychoacoustical measurement (pitch, loudness, minimal masking level, residual inhibition). Hyperacusis is measured according to sound discomfort levels.

Retraining therapy is based on three main topics. First, an exhaustive and wide directive counselling about tinnitus: physiology and pathophysiology of hearing, tinnitus possible aetiology, central auditory pathways, importance of the survival style reflex to maintain tinnitus perception, influence of the limbic system, prefrontal cortex and autonomous nervous system in the tinnitus reaction and annoyance. Second, sound therapy, carried out by environmental sound enrichment, white noise generators and hearing aid devices. Third, relaxation

therapies to reduce anxiety and management of depression and insomnia.

Material and methods

More than 400 patients have been seen in our tinnitus clinic from October 1996 to June 1999. TRT has been offered to the majority of them while only 172 patients have been followed-up. Twenty of them refused sound therapy associated to directive counselling. One hundred and fifty-two accepted full TRT program. Results are evaluated at one year follow-up period (84 cases).

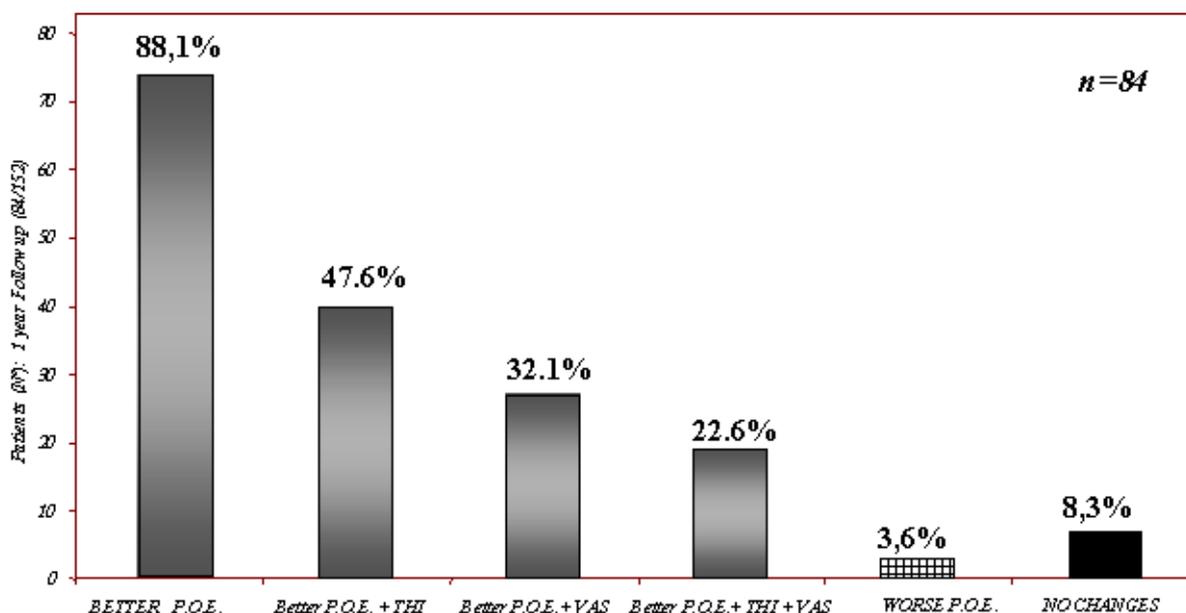
Groups are divided in directive counselling alone (DC), counselling plus sound therapy with white noise generators (WNG) or hearing aids (HA). We considered three outcome measures in our protocol: patient's own evaluation (POE) of the symptom (better, worse, no changes), THI from 0 to 100%, and visual analogical scale score on tinnitus perception intensity (0–10)

Results

Fifty-seven percent were women, 43% men. We use DC alone in 37%, DC plus HA in 46%, DC plus WNG in 37% and two tinnitus instruments (hearing aid with a white noise generator). TRT results are shown in Table 1.

Patients whose tinnitus was not annoying (Jastreboff's category 0) received directive counselling.

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Table 1 Tinnitus Retraining Therapy. 1 year follow-up

This group referred the best results in habituation (93.7%–56.3% considering THI). The group with counselling plus white noise generator, (category 1, 3 or 4) presented a higher relief (83.3%–50% considering THI) if we compare it with counselling plus hearing aid group, category 2, 3 or 4, (84.2%–36.8% considering THI).

Discussion

It has been proved that TRT is a successful approach for tinnitus management in our series. One year follow-up showed that eighty eight percent of the patients referred an improvement in annoyance and perception of tinnitus. The percentage is lower if we consider an improvement in patient's own evaluation (better, worse, no changes) plus a significant difference (upper than 20 points) on THI score. It could be explained due the fact that 85% of the patients presented a THI score better than the initial one, but only the 47.6% of the them had a difference 20 points or more.

The improvement considering changes of 2 or more points in the visual analogical scale on tinnitus loudness was considerably lower (32.1%). Habituation to tinnitus reaction is much more effective than habituation to perception using TRT approach.

If we compare these results with the group that refused sound therapy when recommended (white

noise generators or hearing aids), directive counselling did not get good results in tinnitus habituation (any of the cases improved and 50% were worse)

Conclusion

Patients consider TRT as an effective approach for tinnitus habituation according to their own subjective evaluation. Handicap questionnaires and analogical measurement scales did not show a considerable improvement in this series. These differences could be explained by the high score required to consider THI as significant, and the fact that habituation to tinnitus perception is much lower than tinnitus reaction.

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Tinnitus retraining therapy with bone conductive sound stimulation

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Introduction

Tinnitus is a common symptom occurring in 10–15% of the general population and in 1–2% tinnitus affects the daily life severely [1,2]. Tinnitus is often related to an auditory dysfunction [1,3].

Predictors of tinnitus severity have recently been reviewed [4] and hearing parameters were not found to be strong predictors of the severity of tinnitus. The main predictors to the severity of tinnitus were psychological factors, such as depression and anxiety [4–11], but also physical immobility [4].

Tinnitus retraining therapy (TRT) was introduced by Jastreboff and Hazell [12] and persistent tinnitus was explained as similar to a conditioned response to the perceived tinnitus sound, involving both the limbic system as well as the autonomic nervous system. Jastreboff and Hazell's rehabilitation program is aimed at decreasing this response. The method is based on sound enrichment and a neurophysiologically based counselling program. The sound enrichment is often given by means of an air conductive sound stimulator and an ear mould is placed in the ear canal of the patient.

There are patients with conductive hearing loss who cannot have an ear mould in the ear canal due to different reasons. The primary medical indication for a bone anchored hearing aid (BAHA), f. ex. is that an ear mould can not be used because of a chronic draining ear or malformations. The BAHA is anchored to the skull via a skin-penetrating titanium implant. This is a clinical well-accepted procedure for patients with conductive hearing loss where middle-ear surgery is contraindicated [13,14]. The aim with our present study was to analyse whether it is possible to provide the sound enrichment via bone conduction instead of via an ordinary air conduction sound-stimulator. The ethical committee at the Sahlgrenska University Hospital approved the study.

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Material and methods

Ninety patients with conductive hearing loss, who had been equipped with a BAHA in Göteborg since 1977 when this technique was introduced and were still living in Göteborg, were asked to fill in a tinnitus questionnaire. Eighty-four patients answered the questionnaire and 6 did not, making them dropouts.

Eight patients were selected to be included in a feasibility study to analyse whether it was possible to give low-dose white noise sound stimulation via bone conduction (BAS). The patients were selected due to their different profiles in the audiometrical tinnitus analyses.

It was not possible at the present stage to include a noise generator in the BAHA model, instead a miniaturised bone anchored sound stimulator (BAS) was designed. In the first version of BAS, no microphone was used.

The patients were told to use the BAS at least 6 hours a day.

Results

In the questionnaire, 55% of all BAHA patients in Göteborg experienced tinnitus sometimes and 34% had tinnitus always or often. All 8 patients who were selected for the feasibility study reported that the BAS-generated noise mixed with their tinnitus. Reductions of sleep disturbances were reported when using the BAS. As could be expected, the patients reported on the negative effects of the lack of hearing gain when changing from the BAHA to the BAS.

Discussion

In Göteborg, patients have been operated with BAHA since 1977 and the method is now used in 25 different countries. When relating all 6000 patients operated on world-wide with the finding of 34% tinnitus sufferers (often/always) in the BAHA group in Göteborg, one can conclude that there is a clinical need for a bone conductive noise stimulator.

However, one has to bear in mind that the BAHA has been used in Göteborg during a more extended period and Göteborg may therefore not be fully comparable to other centres. Consequently, our patients may have had their BAHA during a longer time and it is therefore possible that the frequency of presbycusis is higher in our group, which might influence the prevalence of tinnitus.

There are potential advantages with a bone-anchored sound stimulator that can be of significant importance in the rehabilitation of tinnitus in general. It can be anticipated that soundstimulation via bone conduction is different from stimulation via air conduction as both cochleas are stimulated at the same time. This occurs since the bone conducted sound is transmitted throughout the whole skull by use of only one transducer. The significance of this phenomenon must be evaluated in order to investigate whether this is an advantage.

We were unable in this feasibility study to include a low-dose sound stimulator in the standard BAHA due to technical reasons, but in future models of the BAS a microphone will most likely be incorporated.

Conclusions

Low-dose white noise sound stimulation can be transmitted via bone conduction. Our preliminary data reveal that the annoyance of tinnitus can be reduced by this procedure.

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Questionnaires for assessment of the patients and treatment outcome

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No objective method currently exists for detecting the presence of tinnitus and hyperacusis or for assessing their severity. As a result, it is crucial to develop and implement a consistent method for the initial characterization of a patient and for following potential changes during treatment. A set of questionnaires is commonly used to achieve these goals, however, there is not a uniform set of questions and various groups are using different sets of questionnaires. Our goal is to create questionnaires which will: (1) assess the impact of tinnitus and hyperacusis on a patient's life; (2) observe changes during the treatment; (3) provide estimation of the presence and extent of habituation; and (4) can be used, with minimal modification, for patients in a variety of countries around the world. Fulfilling the last requirement will enable an effective comparison of the results of various centers and aid in the creation of an international database. Ultimately, this type of questionnaire would significantly facilitate the understanding of tinnitus, hyperacusis and the development of an effective method for controlling each condition. On the basis of information from literature and our personal experience with patients, we have developed a set of questionnaires which will be presented for discussion.

Tinnitus, a symptom dating back to ancient times, affects a large population of people around the world. Continuous efforts in development of medical, surgical, psychological and rehabilitative treatments and experimental research have failed to provide a cure or a generally approved management program for patients suffering from tinnitus. In addition, science has not produced an objective measure to detect the presence of tinnitus or to assess its severity, and consequently, the evaluation of any tinnitus treatment outcome is based on subjective evaluation of the problem. Descriptive questionnaires can be very useful in everyday practice when working with individual patients. However, this type of questionnaire often lacks precision and objectivity and is not only time consuming, but also difficult to evaluate when attempting to combined the results of different providers. Recognizing time restrictions in today's medical practice and the need for more efficient evaluation of different treatments have encouraged us to develop a new, easier and more objective forms for providers to use in their practices. Ultimately, this information could be supplied to a multi-center database, and would enable us more efficiently analyze results from a large population of tinnitus patients.

Based on our experience, self-report measures and scales, and a study of comprehensive questionnaires, we have developed initial and follow-up forms for structured interviews, that we believe are very useful in obtaining core information from patients without overwhelming them with unnecessary questions at the time of their visit. In addition, the information gathered with the use of these forms is not only useful during treatment, but also in evaluation treatment outcome. These forms are supplemented by information received from medical and tinnitus history expanded questionnaires sent to prospective patients before their initial visit. Additionally, the Tinnitus Handicap Inventory [1] is administered to individuals during their visits to the Center. Our choice of questionnaires does not preclude the use of other measures and methods to obtain information from tinnitus and hyperacusis patients, depending on personal preference of a provider.

Presented below are forms that we developed for the management of patients with tinnitus and/or hyperacusis and/or hearing problems, when applying Tinnitus Retraining Therapy (TRT). Obviously, these forms can potentially be used for evaluation of patients undergoing other types of treatment as well, but they were planned to include an assessment of habituation of tinnitus. These forms serve as easy guidelines when used during initial interviews, audiological or medical evaluations, and counseling, and are helpful in evaluating the pro-

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gress of treatment. Notably, the information from these forms can easily be transferred to a database and thereby allow for efficient data analysis.

To assure non-biased responses, all questions are asked of all patients in a neutral, consistent manner and in the same way to all of the patients, even if any of their responses might be known to us from an earlier conversation. Some questions may raise the need for additional explanation or clarification. We have found during interviews that when a questionnaire is given to a patient to take home, the questions are frequently misunderstood and answered in a variable manner. This occurs even when additional descriptive explanations of the questions have been provided. We therefore conclude that a structured interview, with the form serving as a guidance tool to the questions, is the best way to acquire information from a patient. Moreover, to avoid a bias of responses, neither forms nor results should be distributed to patients to take home.

The forms consist of four parts aimed at the evaluation of tinnitus, hyperacusis, hearing problems, and for general ranking of the reported complaints. As a significant number of patients with tinnitus are also affected by increased sensitivity to sound, this necessitates use of a separate section related to hyperacusis.

An initial interview in our Center begun by assessing the main problem reported by the patient. Detailed questions are not asked when a problem is not reported by the patient or detected during medical or audiological evaluation. Repetitive answers from the patient (e.g., ear protection when patient has both tinnitus and hyperacusis) are marked on the forms without repeating the questions.

The TRT outcome is predominantly measured by evaluating changes in awareness, severity, annoyance, effect on life and by monitoring activities prevented or affected by tinnitus and/or hyperacusis [2]. Other factors (e.g., ear overprotection) and questions (e.g., frequency of bad days) are very helpful in monitoring the progress of a treatment, but these factors do not play a significant role in evaluating the prognosis of the treatment outcome. We are continuing to work on the evaluation of analog scales, if found to be more reliable, to potentially replace the numerical 0–10 scale. Typically, the gradation of the grey-blue colors is used and, with the numerical scale provided for the counselor on the reverse side.

The information that we acquire from these forms is entered into a database. This database was created for everyday use and to facilitate a multi-center study of TRT efficacy. It is very difficult for one center to validate TRT in a reasonable period of time for several reasons. First, there is not a clear control group, and due to significant awareness

about the TRT protocol among patients, it is very difficult to randomize the patients into TRT and placebo groups. Secondly, both counseling and the use of sound, are integral parts of TRT. Separating these two components and using only one of them for different groups would not provide a realistic evaluation of TRT. Finally, TRT requires a serious time commitment from health providers to individual patients and treatment can take approximately 18 to 24 months to complete. Therefore, it would take a long time for one center to acquire and evaluate statistically significant results from a sufficiently large population of patients. Recently, a study comparing the effectiveness of masking and TRT has been started (J Henry, VA Grant No. C2299RC) and within 3 years should provide an assessment of the relative effectiveness of these approaches, but will not enable a direct comparison of the treatment versus untreated control.

With our experience of over 1000 patients, we discovered that a significant portion of the patients are using other methods (e.g., relaxation techniques, the use of some herbal medicine, acupuncture, etc.) simultaneously with TRT to improve their well-being and to lessen the distress caused by tinnitus. Following guidelines of the neurophysiological model of tinnitus, such supplementary treatment is encouraged and should facilitate tinnitus habituation provided by TRT. We are monitoring patients who independently decide to try supplementary treatment simultaneously with TRT in attempt to thoroughly assess the possible contribution of supplementary treatments to the final outcome of TRT.

In conclusion, we believe that the use of our questionnaires as a standard, and the collection of data in a multi-center database will aid in the analyzation of results obtained from many centers with variable, random populations of patients who represent different cultural and social backgrounds and who are involved in varying medical systems. Furthermore, in a continued effort to provide reliable evidence for the validity of TRT, these results will be obtained without a pre-selection of patients and by each patients deciding whether to accept a proposed treatment.

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**TINNITUS / HYPERACUSIS
INITIAL INTERVIEW FORM**

Clinic # :
Name :
DOB :
SSN :
Insurance :
Date :

T&HC#:

tel:
e-mail:

RE / LE / Both / Head = > Intermittent / Constant
Onset: Gradual / Sudden When
Fluctuations in volume Y / N "Bad days" Y / N Frequency

Description of T sound(s)

T
I
N
N
I
T
U
S

Activities prevented or affected:
 Concentration Sleep QRA Work
 Restaurants Sports Social Other

Effect of sound: None / Louder / Softer
How long: min / hours / days

% of time when: Aware Annoyed
Severity: 0 1 2 3 4 5 6 7 8 9 10
Annoyance: 0 1 2 3 4 5 6 7 8 9 10
Effect on Life: 0 1 2 3 4 5 6 7 8 9 10

Ear overprotection Y / N % of time
in quiet Y / N
Any other T specific treatments
Why is T a problem

Comments:

S
O
U
N
D

T
O
L
E
R
A
N
C
E

Oversensitivity: Y / N Physical discomfort? Y / N
Description of troublesome sounds

"Bad days" Y / N Frequency

Activities prevented or affected:
 Concerts Shopping Movies Work
 Restaurants Driving Sports Church
 Housekeeping Childcare Social Other

Effect of sound: None / Stronger / Weaker
How long: min / hours / days

Severity: 0 1 2 3 4 5 6 7 8 9 10
Annoyance: 0 1 2 3 4 5 6 7 8 9 10
Effect on Life: 0 1 2 3 4 5 6 7 8 9 10

Ear overprotection Y / N % of time
in quiet Y / N
Any other ST specific treatments
Why is ST a problem

Comments:

Hearing problem Y / N
Hearing Aid(s) Y / N type:
Ever recommended Y / N

Category:
Recommendation:

Ranking problems: Tinnitus: 0 1 2 3 4 5
Sound tolerance: 0 1 2 3 4 5
Hearing: 0 1 2 3 4 5

Ptn decision:
Next visit:

T - tinnitus ST - sound tolerance (hyperacusis + phonophobia)
Is you T preventing or affecting any activities in your life.
QRA - quiet recreational activities: Is your T interfering with QRA such as reading or meditating.
% of time when: **Aware** - What % of time were you aware of your T over last month?
Annoyed - What % of the time over last months T bothered you?
Severity - How strong or loud is your T on average over last month? 0 - no T, 10 - as strong as you can imagine.
Annoyance - How much was T annoying you on average over last month 0 - not at all; 10 - as much as you can imagine.
Effect on life - How much was T affecting your life on average over last month. 0 - no effect; 10 - as much as you can imagine.
Any other T specific treatments - Are you using any other treatments for your T.
Sound tolerance - Is your tolerance to louder sounds the same as people around you?
Hearing - Do you think you have a hearing problem?
Ranking - rank importance of your problems with 0 - no problem, 5 - as large as you can imagine
MM & PJ Jastreboff,
1999



**TINNITUS / HYPERACUSIS
FOLLOW-UP INTERVIEW FORM**

T&HC#: CATEGORY:
Date of init. couns.
Date of instr. fitt.
tel: SG:
HA:
FUQ #:
Month #:

Clinic # :
Name :
DOB :
SSN :
Insurance :
Date :

T
I
N
N
I
T
U
S

Activities prevented or affected: Changes: Y / N
 Concentration Sleep QRA Work
 Restaurants Sports Social Other
 % of time when: Aware (1st) Annoyed (1st)
 Has it changed
 Severity: 0 1 2 3 4 5 6 7 8 9 10
 Annoyance: 0 1 2 3 4 5 6 7 8 9 10
 Effect on Life: 0 1 2 3 4 5 6 7 8 9 10

"Bad days" Y / N Frequency
 Are they: as frequent Y / N as bad Y / N
 Effect of sound: None / Louder / Softer
 How long: min / hours / days
 Ear overprotection Y / N % of time
 in quiet Y / N
 Any other T specific treatments

Comments:

S
O
U
N
D
T
O
L
E
R
A
N
C
E
H
L

Description of troublesome sounds
 Activities prevented or affected: Changes: Y / N
 Concerts Shopping Movies Work
 Restaurants Driving Sports Church
 Housekeeping Childcare Social Other
 Severity: 0 1 2 3 4 5 6 7 8 9 10
 Annoyance: 0 1 2 3 4 5 6 7 8 9 10
 Effect on Life: 0 1 2 3 4 5 6 7 8 9 10

"Bad days" Y / N Frequency
 Are they: as frequent Y / N as bad Y / N
 Effect of sound: None / Stronger/ Weaker
 How long: min / hours / days
 Ear overprotection Y / N % of time
 in quiet Y / N
 Any other ST specific treatments

Comments:

Hearing problem

Recommendation:

The problem in general: Same / Better / Worse
 Ranking problems: Tinnitus: 0 1 2 3 4 5
 Sound tolerance: 0 1 2 3 4 5
 Hearing: 0 1 2 3 4 5

Next visit:

How would you feel if you had to give back your instruments
 Are you glad you started this program? Y / N / NS

Main problems discussed:

T - tinnitus ST - sound tolerance (hyperacusis + phonophobia)
 Is you T preventing or affecting any activities in your life. ●○ - an activity affected at first visit
 QRA - quiet recreational activities: Is your T interfering with QRA such as reading or meditating. ○● - an activity affected as for today
 % of time when: **Aware** - What % of time were you aware of your T over last month?
Annoyed - What % of the time over last months T bothered you?
Severity - How strong or loud is your T on average over last month? 0 - no T, 10 - as strong as you can imagine.
Annoyance - How much was T annoying you on average over last month 0 - not at all; 10 - as much as you can imagine.
Effect on life - How much was T affecting your life on average over last month. 0 - no effect; 10 - as much as you can imagine.
Any other T specific treatments - Are you using any other treatments for your T.
Sound tolerance - Is your tolerance to louder sounds the same as people around you?
Hearing - Do you think you have a hearing problem?
Ranking - rank importance of your problems with 0 - no problem, 5 - as large as you can imagine
 MM & PJ Jastreboff, 1999

Optimal sound use in TRT – theory and practice

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Tinnitus Retraining Therapy (TRT) consists of two main components: retraining counseling and sound therapy. Retraining counseling is oriented toward removing the patient's negative associations with tinnitus. This is accomplished by educating the patient that his/her tinnitus results from a normal compensatory mechanism, which occurs in the auditory system, to typically minor changes in the cochlea. As a part of counseling, it is also important to demystify the mechanisms through which tinnitus may affect a patient's life. Sound therapy is aimed at facilitating the process of habituation of both tinnitus-induced reaction and tinnitus perception by decreasing the difference between tinnitus-related neuronal activity and background neuronal activity. Since all our senses work on the basis of differences between signals and background, and not on its absolute value, by decreasing the difference between the tinnitus signal and the background neuronal activity it is easier for the central nervous system to filter out or block tinnitus-related activity.

This, however, presents only one of several neurophysiological mechanisms relating the effectiveness of habituation to sound level used during sound therapy. As clinical and experimental data show, there is no need to tune the spectrum of the external sound to cover the pitch of tinnitus. The requirement is that the sound be relatively broad. In practice, the effective spectrum range of majority of sound generators is about two octaves, and typically below the prevalent pitch of tinnitus. This is one of the reasons for the recommendation for the constant use of enriched environmental sound in addition to sound generators. Furthermore, blockage of the ear canal caused by in-the-canal hearing aids, should be avoided to prevent attenuation of low frequency environmental sound.

Another aspect, reflecting the dynamic balance principle governing neuronal plasticity indicates the benefits delivered from continuous, rather than intermittent sound exposure, and from the use of sound during sleep. Plastic reorganizations of neuronal connections also argue for the use of symmetrical stimulation or for restoring this symmetry whenever it is possible. Modification of the original tinnitus signal, which occurs during partial suppression ("masking"), and its removal during total suppression, results in decreased or total ineffectiveness of the sound used for promoting habituation. On the other hand, using a sound level below or at the threshold of hearing is not recommended either. For tinnitus and hyperacusis, use of sound follows the principle of passive extinction of the conditioned reflexes, linking tinnitus-related neuronal activity within the auditory pathways with responses of the limbic and autonomic nervous systems. The reversal of phonophobia requires positive reinforcement achieved by associating gradually increased sound levels with pleasant situations. Finally, the sound used should not induce annoyance or negative reactions. All of these factors, further influenced by the specific category of the patient, determine the version of the optimal sound therapy as well as requirements for the parameters of instrumentation.

Sound therapy is an integral part of tinnitus retraining therapy (TRT). The counseling component of TRT is aimed at changing classification of tinnitus, removing its negative connotation, and creating a condition for habituation to occur. The process of habituation is then promoted and facilitated by the use of sound which is aimed at decreasing the difference between the tinnitus signal and background neuronal activity. Through this decrease, the strength of tinnitus signals circulating within feedback loops connecting all the centers in the brain involved in tinnitus are also decreased. For each category of patients, the protocol of sound use is different and the methods of sound delivery can vary substantially.

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There are certain recommendations of sound therapy which are common for all categories of patients: (1) all patients are advised to avoid silence and use enhanced background sound; (2) exposure to sound levels which result in annoyance or discomfort, when present for prolonged periods of time, should be avoided; (3) the sound level patient uses should not suppress ("mask") tinnitus, either totally or even partially; (4) sound should be used for the longest duration possible, even at the expense of lowering its intensity, rather than using higher levels of sound for shorter periods of time, as indicated by the dynamic balance principle of the neurophysiological model; (5) sound should be used through the night, as lower levels of the auditory pathways are very active during sleep, and due to periodic pattern of sleep levels.

Because the sound has to be listened to for many hours, the majority of people find it is easier to tolerate the sound when it does not have meaning, is should be neutral and does not induce an emotional reaction. Radio and television contain speech which attracts attention. Music, on the other hand, induces strong emotions, and may attract attention as well. While some patients can adopt to a low volume of radio, television, or music, others find meaningless sound, such as broadband noise or the sounds of nature to be easiest to accept. Such sounds can be produced by sound generators, played on a CD player (e.g., sound of nature), or synthesized a tabletop sound machine.

It is important to analyze the theoretical relationships existing between the physical intensity of sound and its effectiveness on tinnitus habituation (Figure 1). Five factors influence this relationship: (1) stochastic resonance (enhancement of the signal by adding low level noise); (2) dependence of the signal's strength on its contrast with the back-

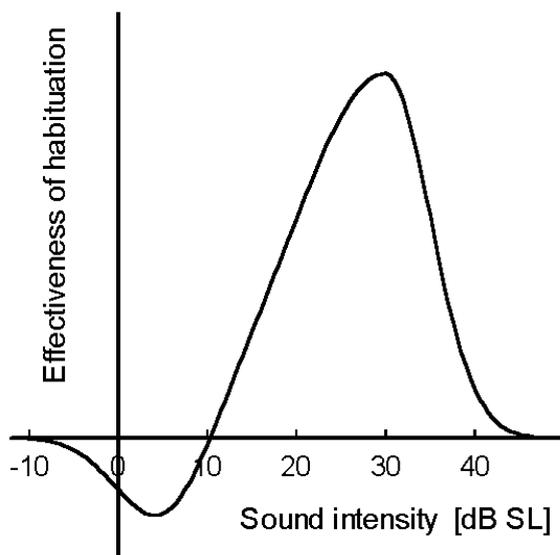


Figure 1 Functional dependence of habituation effectiveness on physical intensity of a sound. Notice the need to avoid sound levels close to threshold of hearing and those inducing partial or total suppression.

ground; (3) total suppression of the signal preventing any retraining and consequently habituation; (4) partial suppression ("partial masking") which does not prevent retraining but does make it more difficult, as the training is performed on a different stimulus than the original; (5) activation of limbic and autonomic nervous systems by too loud or unpleasant sounds yielding increase of tinnitus and contracting habituation.

Let us discuss the combined effects of these factors. If the sound level is significantly below the threshold level of detection there is no basis to believe that it asserts any effect on the auditory system and tinnitus. On the other hand, when external sound becomes strong enough to suppress detection of tinnitus-related neuronal activity, by definition, any kind of retraining (including habituation) or changing reactions to tinnitus is prevented, because the brain cannot change reactions to a stimulus it cannot detect.

When the sound level is still below, but close to the threshold of detection, the phenomenon of stochastic resonance comes into play [1,2] (for details see [3]). On the basis of results obtained from the stochastic resonance of the hair cell system, and from the recordings from the cochlear nerve, it is possible to expect that the effective sound level inducing stochastic resonance covers a range of about 15–20 dB, beginning from about –5 dB below the threshold of detection of the original signal. Thus, due to stochastic resonance, by adding low level external noise paradoxical enhancement of the tinnitus signal occurs. A weak tinnitus signal, which could not be detected in silence, can be observed by adding external noise. Additionally, the tinnitus signal which has been detected in silence will undergo enhancement. Consequently, tinnitus perception could be enhanced by adding low levels of sound, such as in case of using sound generators set at the threshold of hearing or just slightly above the threshold. This will in turn make habituation more difficult.

Of note, stochastic resonance is highly individual and its specifics depend upon the degree of hearing loss and the strength of the tinnitus-related neuronal activity. Nevertheless, for a vast majority of the patients, the tinnitus signal is relatively weak, as indicated by the low level of its intensity match. Therefore, stochastic resonance could play an important role. The neglect of this phenomenon and the use of levels of the sound that are too low can be detrimental to the process of habituation.

Results of the study in which a comparison was performed among groups with counseling only (including advice of using environmental sounds), counseling combined with sound generators set at the threshold of hearing, and with counseling combined with sound generators set at close to "mixing" point, fully support the prediction of the importance of stochastic resonance. The group that performed the worst was the one with the sound level set close to the threshold of hearing, while the best group was with the sound level set at "mixing point," with counseling only group in the middle [4].

When sound level is further increased, the mechanism involving the decreased difference between the tinnitus signals and background neuronal activity becomes the dominant factor. As in all nervous system, the absolute physical intensity of a stimulus is secondary for the effective strength of the signal. The difference between the signal and the background plays the dominant role. By decreasing the difference between the tinnitus-related neuronal activity and the background ongoing neuronal activity, the effective strength of the tinnitus signal decreases and this weaker signal is passed to the higher level cortical areas, and most importantly, to the limbic and autonomic nervous systems. This helps in initiating and sustaining the process of passive extinction of conditioned reflexes which link tinnitus to negative reactions (further discussed in accompanying papers [3,5]). As the background activity is the sum of spontaneous and evoked activities, the differences between the tinnitus signal and the background activity can be achieved by exposing patients to additional external sound.

This principle, if working alone, would imply that we should use a sound that is as intense as possible. However, two other factors (3 and 4) become dominant. First, once the tinnitus signal is suppressed, habituation will not occur by definition, due to the lack of a signal to habituate (principle 3). When the sound level surpasses the threshold of partial tinnitus suppression (“partial masking”), this will modify not only the intensity, but also the quality of the tinnitus signals. Then, retraining of neuronal networks will occur to the modified tinnitus signal and not to the original one. Due to the generalization principle (e.g., reaction can be induced to stimuli similar to the original, with the strength depending on the difference between the original and the modified signals), some habituation may still occur. The higher the external sound is above the threshold of partial masking, the smaller its contribution to habituation. Finally, once a level of total suppression is reached, the effectiveness of habituation is decreased to zero, as the brain cannot retrain to a signal which it cannot detect.

It is instructive to assess the potential range of influence exerted by these factors. As evident from this description, the effective range of external sound to be used for tinnitus habituation is between the level which is above the range of stochastic resonance effect (approximately 10–15 dB above the threshold of hearing) and the beginning of partial suppression (described by patients as a “blending or mixing” point). At this point patients are still able to separate the blend of tinnitus and external sound into their individual components. Our measurements of sound levels used by patients performed during evaluation of Viennatone (AM/Ti and Silent Star) and General Hearing Instruments (Tranquil) sound generators, as well as the real ear measurements performed for these devices, revealed the level to be typically about 30 dB above the threshold of hearing. Thus, we have approximately 15–20 dB of dynamic range for positive action of sound generators.

For the low sound levels which we use, the just noticeable intensity difference is about 2.5–3 dB, giving about 10 steps up to the “mixing point.” However the first three to five steps from the hearing threshold should be excluded due to the effect of stochastic resonance. Consequently, the approximate sound level to be avoided cover the lowest 1/3 of the range below the “mixing point” (Figure 1). Please note, that using a sound level that is too low could be, paradoxically, worse than using no sound at all.

The optimal setting of the sound level is different when hyperacusis is the dominant, or the only problem. In this situation, the effect of stochastic resonance is of secondary importance comparing with the need to not overstimulate the auditory system. The patient starts with a sound level close to his/her threshold, but as high as sound sensitivity allows, aiming to be above the range of stochastic resonance. If this cannot be initially achieved due to very low sound tolerance, patients should be instructed that their tinnitus might initially increase.

Once a partial reversal of hyperacusis is achieved, the sound level can be increased rapidly to directly address tinnitus. Rules previously described for tinnitus patients should be followed at this point. Patients exhibiting a “winding-up” effect should be treated with separate attention. Once hyperacusis is under at least partial control, the issue of phonophobia, if present, should be addressed. We recommend the use of sound according to the principle of active extinction by associating perception of sounds with positive reinforcement.

The sound spectrum of sound generators is not crucial. The results of Feldmann on tinnitus masking and our results with single unit activity [6] indicate that tinnitus can be similarly affected by sounds from a wide frequency range. However, it is still beneficial to provide the patient with stimulation of a wide range of neurons in the auditory pathways corresponding to those frequencies. Since the sound generators which are currently available have a restricted spectrum of sound, and are unable to provide the stimulation for frequencies below 500 Hz, patients are always advised to enrich their auditory environment.

The need to preserve stimulation in the low frequency range yields a strong recommendation for people who have relatively normal low frequency hearing, to be provided with devices or hearing aids with fitting as open as possible. It is not sufficiently appreciated that in the normal acoustic environment there is a high proportion of low frequency sounds, below 200 Hz, which provide constant stimulation of the auditory pathways. Since the majority of patients have relatively normal hearing in this frequency range, they benefit from this stimulation. Consequently, blocking the ear canal by closed ear molds decrease the auditory input, and many patients experience the enhancement of tinnitus when their ears are blocked.

Note that even the best hearing aids act as ear plugs in low frequencies when they are in-the-canal type or are fit with a closed mold, as they are unable

to reproduce frequencies below 200–250 Hz due to restriction based on the physics of sound generation by a loudspeaker. Accordingly, the requirement for preserving stimulation of environmental sounds in the low frequency range results in a recommendation not to use in-the-canal hearing aid, and in recommendation of using as open as possible ear molds, even at the expense of decreasing the maximal gain available. Note, that hearing aids for tinnitus patients are used mainly as a part of sound therapy to provide extra amplification of background sounds, and only secondary for communicative purposes.

In summary, proper use of sound therapy as a part of TRT can offer significant help, although there is no one simple recommendation regarding the use of the sound that could be applied to all tinnitus and/or hyperacusis patients (except a general statement of avoiding silence). Proper diagnosis and categorization of the patients are crucial for choice and proper implementation of specific protocol of sound use. Note, that it is sound that is important and not any particular device. Depending upon the category of a patient and his/her individual needs, the use of sound should be governed by different rules with adjustment of the sound according to the category of treatment.

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Audiometrical characterization of hyperacusis patients before and during TRT

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The neurophysiological model of tinnitus predicted that decreased tolerance to a sound should accompany tinnitus in significant proportion of cases [1]. Clinical results revealed that indeed it exists in approximately 40% of cases, and requires specific treatment in about 25% of all our patients. Increased sound sensitivity is an abnormally high sensitivity to a sound resulting from the sum effects of hyperacusis and phonophobia which can be defined as follows:

Hyperacusis – abnormally strong reactions occurring within the auditory pathways resulting from exposure to even a moderate sound level. Consequently patients express reduced tolerance to sounds above threshold of hearing.

Phonophobia – abnormally strong reactions of the autonomic and limbic systems without abnormally high activation of the auditory system resulting from enhanced connections between auditory and limbic system. Consequently, patients are afraid of sound.

In practice hyperacusis and phonophobia can appear separately or accompany each other. If hyperacusis is present, it has to be treated first. Moreover, hyperacusis and phonophobia require a different method of treatment. Therefore, their proper characterization is crucial for the successful treatment with Tinnitus Retraining Therapy (TRT). When applied properly, TRT is highly effective for the treatment of hyperacusis and phonophobia, and these patients tend to show faster recovery time with higher rate of successful outcome than those solely with tinnitus.

Basic audiometric measurements which help in delineation of hyperacusis, and separate it from phonophobia, are pure tone Loudness Discomfort Levels (LDLs), with its comparison to the expanded frequency audiogram, plus high resolution distortion products otoacoustic emission (DPOAE). However, a detailed interview is always necessary.

Some hearing loss is present in the majority of patients. The comparison of the audiogram with LDLs provides a tool for determining the presence of pure hyperacusis, pure phonophobia, or the combination of both. As pure hyperacusis involves only the auditory system, reaction to sound depends on its physical parameters (intensity in dB SPL, spectrum) and not on the context in which it appears. Consequently, LDLs are flat with a tendency of lower values (in dB HL) for low and high frequencies, and they are independent of the audiogram shape. As pure phonophobia depends upon the connections of the auditory system with the limbic system and its reaction, patients' reactions will depend upon the perceived loudness of the sound (dB SL) and its context, and secondary to its physical characterization. Consequently, LDLs follow the shape of the audiogram. Individual cases will be presented to demonstrate various subtypes, and the averages of audiogram, and LDLs will provide general characterization of the population of hyperacusis patients.

It is possible to indicate several peripheral and central mechanisms of hyperacusis. Certain types of peripheral hyperacusis can be detected by examination of the DPOAE which may exhibit abnormally large amplitude or abnormal input-output function. Such cases have been observed in the population of patients treated at the University of Maryland. Furthermore, if these patients belong to Category 4 (characterized by prolonged worsening of their symptoms by the exposure to sound) then they can be treated by an aspirin protocol, in addition to applying TRT [8].

During treatment with TRT it is possible to expect some central modification within the auditory pathways, as well as peripheral changes in the cochlea, which might depend on similar mechanisms

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as auditory toughening. Indeed, experiments performed in our laboratory on rats with the use of sound levels similar to those used by our patients show a strong protective effect for both total transduction of the cochlea and for OHC [9]. At the clinical level, results from University of Maryland as well as those from London Clinic, show that LDLs exhibit systematic increases during the treatment, which correlates to subjectively perceived improvement.

Increased sound sensitivity, described as abnormally high sensitivity to sound, or as a decreased sound tolerance, is a known but vastly underestimated problem. There are no epidemiological studies describing prevalence of the problem in the general population. Some preliminary information about the prevalence of sound sensitivity in the population of patients with clinically significant tinnitus is available, but various centers reported results which were contradictory in nature [1–3]. There is a large need to assess at least to which extent increased sound sensitivity plays role in population of patients who are coming to otolaryngological or audiological practice.

Increased sound sensitivity is a result of two effects: (1) hyperacusis, representing abnormally strong reactions occurring within the auditory pathways to the exposure to even moderate sound; and (2) phonophobia, representing abnormally strong reactions of the limbic and autonomic nervous systems without any abnormally high activation of the auditory systems, resulting from enhanced connections between the auditory and limbic systems.

Hyperacusis patients express reduced tolerance to supra-threshold sounds, frequently ordinary, environmental sounds. The loudness discomfort levels (LDL), determined for a number of frequencies to pure tones, offer an estimation of the sound tolerance. The incidence of hyperacusis in a population of approximately 1,000 patients treated at the University of Maryland Tinnitus and Hyperacusis Center (1990–1998) was as high as 40% [1], with 27% (44 out of 163) of patients with tinnitus, who were more affected by their hyperacusis than tinnitus. Hyperacusis is frequently accompanied by phonophobia, described as discomfort to special environmental sounds and the patients express fear of specific sounds. Both of these phenomena can also appear separately, but in case of significant hyperacusis phonophobia is practically inevitable. Tinnitus and hyperacusis share a common mechanism of increased central or peripheral auditory sensitivity [4,5].

Hyperacusis and phonophobia require different protocols of treatment. When applied properly, Tinnitus Retraining Therapy (TRT) is highly effective for the treatment of both symptoms, with hyperacusis patients usually showing a faster recovery, and a higher rate of successful outcomes than tinnitus patients [1,6].

Since hyperacusis, phonophobia, and tinnitus require different approaches and hyperacusis has to be treated first [1,5,6], proper evaluation is of crucial importance. Basic audiometrical evaluations, which help in the delineation of hyperacusis and in

separating it from phonophobia, are pure tone LDLs, together with their comparison to extended frequency audiograms, and high resolution distortion products otoacoustic emission (DPOAE). The measurements are not sufficient for diagnosis, and a detailed interview is necessary to assess the extent of sound sensitivity, and its components. Forms used as guidelines during interview are important to assure that all crucial information is gathered before determining the treatment and for monitoring behavioral changes during treatment [7].

Some hearing loss, typically in the high frequency region, is present in the majority of patients. The comparison of the audiogram with LDLs provides a tool for determining the presence of pure hyperacusis, pure phonophobia, or a combination of both. As pure hyperacusis involves only the auditory system, reaction to sound depends upon its physical parameters (intensity in dB SPL, spectrum) and not on the context in which sound appears. Consequently, LDLs are flat with a tendency of lower values (in dB HL) for low and high frequencies, and they are independent on the shape of the audiogram. As pure phonophobia reflect increased level of connections of the auditory system with the limbic system and limbic system reactivity, patients' reaction will depend upon the perceived loudness of the sound (dB SL) and only secondary to its physical parameters. Consequently, LDLs follow the shape of the audiogram.

It is possible to indicate several peripheral and central mechanisms of hyperacusis. Certain types of peripheral hyperacusis can be detected by examination of the DPOAE, which may exhibit abnormally large amplitude of response, or abnormal input-output functions. Such cases have been observed in the population of patients treated at the University of Maryland. Furthermore, if these patients belong to Category 4 [6], characterized by prolonged worsening of their symptoms by exposure to sound, then they can be treated by an aspirin protocol [8], in addition to applying TRT.

During treatment with TRT, it is possible to expect some central modification within the auditory pathways, due to induced plastic modification by the prolonged presence of enhanced sound background. Moreover, at the periphery, in the cochlea, some modification might occur based on similar mechanisms as the auditory toughening. Experiments performed in our laboratory on rats with the use of sound levels close to those used typically by our patients showed a strong protective effect for both total transduction of the cochlea, and functional integrity of outer hair cells [9].

Before going into detailed analysis of the poten-

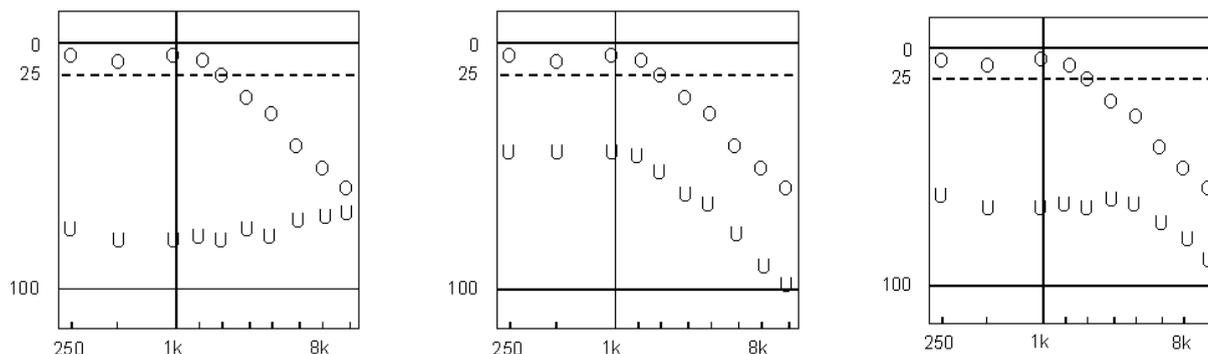


Figure 1 An example of hearing thresholds and LDLs for pure hyperacusis, pure phonophobia, and typically occurring mixture of both.

tial mechanisms of sound sensitivity, it is crucial to provide a basic audiological characterization of an average population of patients. As a part of routine the audiological evaluation, threshold of hearing and loudness discomfort levels have been determined for 0.1, 0.25, 0.5 1, 2, 4, 6, and 8 kHz, together with the most comfortable and uncomfortable levels for speech. Out of 809 patients included in this report, for 53.8% tinnitus was a primary complaint, for 19.8% hyperacusis and tinnitus, 24.4% had only hearing loss, and 2% did not have any specific problem. Note the 26.9% prevalence of hyperacusis among patients with tinnitus. This value is nearly identical with previous estimates obtained from totally different population of patients (27.0% of 163 cases).

The average audiogram for all patients (Figure 2) confirms a postulate that a significant proportion of patients have normal hearing for low frequency range, with clear indication of high frequency hearing loss. This observation has a profound impact on

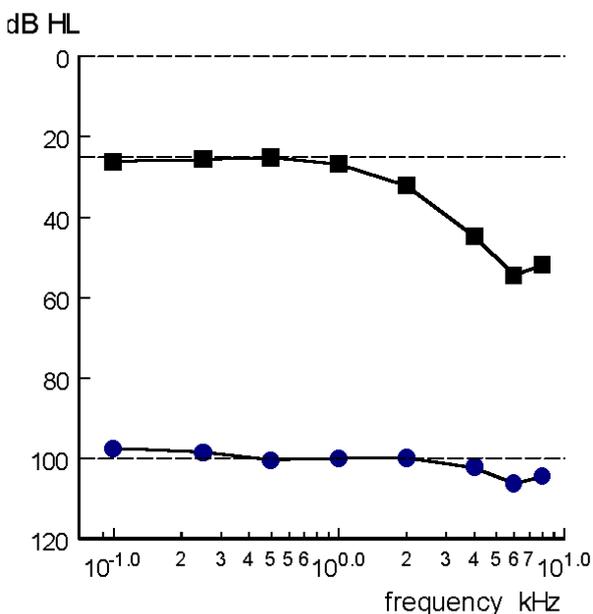


Figure 2 An average audiogram (squares) and LDLs (circles) for all patients.

the practical aspects of TRT, as it argues strongly against using in-the-canal hearing aids or close molds when sound generators of hearing aids are used as a part of sound therapy [1].

Another interesting observation is flat curve describing LDLs, very close to 100 dB HL level. This value has been proposed on the basis of preliminary data, to be used as a criterium of potential sound sensitivity. Data presented here support validity of accepting 100 dB HL level of LDL as a borderline for sound sensitivity, however, better insight into functional properties of the auditory system can be obtained by comparative analysis of the distribution of average hearing, LDLs, and speech most comfortable and discomfort levels (Figure 3).

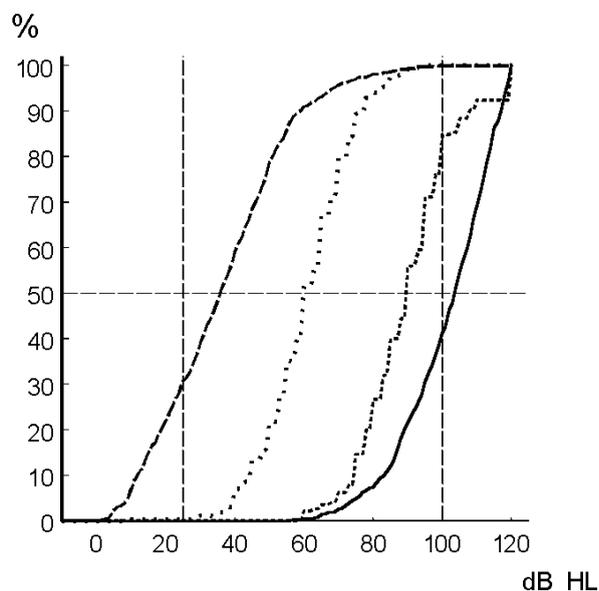


Figure 3 Cumulative distributions of average thresholds of hearing (dashed line), LDLs (solid line), speech most comfortable level (dotted light line), and discomfort level for speech (dotted 8 line). Horizontal line at 50% indicate the median for a given parameter. Vertical line at 25 dB HL indicate the border for normal hearing, and vertical line at 100 dB HL indicate proposed border for sound sensitivity.

Smooth cumulative distribution of average hearing thresholds, with saturation observed for values above 50 dB HL indicate the presence of two relatively homogenous populations with borderline separating them around 50 dB HL. Note, that 30.7% of the patients have average hearing lower than 25 dB HL showing that at least 30% of this population of patients have normal hearing.

Median for LDL is 103.5 dB HL, with 41.2% of patients have an average LDLs lower or equal 100 dB HL. An interesting discrepancy exists between distributions for LDLs and discomfort level of speech. This last distribution is shifted toward lower values with median of 89.5 dB HL, what together with observation that distributions for most comfortable and uncomfortable levels are closely parallel, indicating the possibility of speech discomfort level being stronger influenced by subjective perception of perceived loudness above sound considered optimal and as such stronger affected by phonophobia. LDLs might offer better assessment of the hyperacusis component. Analysis of the relationship of the speech uncomfortable levels versus the average LDLs showed the presence of positive correlation, but high level of variability precludes making valid estimation of one variable on the basis of the other.

The evaluation of the distribution of above parameters for each patient category confirmed predicted trends. Furthermore, LDLs systematically decreased during treatment. To achieve valid estimation of the sound sensitivity it will be crucial to embark into multi-center studies, and to combine results from a number of centers.

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Changes in loudness discomfort level and sensitivity to environmental sound with habituation based therapy

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Around 40% of individuals with tinnitus are also reported to have hyperacusis [1,2]. The prevalence of phonophobia (discomfort to specific environmental sounds) in individuals with tinnitus has not been documented. Tinnitus and hyperacusis are proposed to share a common mechanism of increased central auditory sensitivity [3,4].

Tinnitus retraining therapy (TRT), which is a form of habituation based therapy (HBT), includes a specific desensitisation programme for hyperacusis using noise generators (NGs). NGs are also used as part of a sound therapy programme in the treatment of tinnitus.

The aims of this study were three-fold:

- 1 To determine whether changes in tinnitus related reaction and perception were related to changes in hyperacusis and phonophobia.
- 2 To determine whether changes in hyperacusis and phonophobia were greater in those individuals treated with NGs than those who were not.
- 3 To determine whether changes in sound sensitivity occurred in distressed individuals who did not receive treatment for their tinnitus.

Changes in loudness discomfort levels (LDLs) to wide band noise (measuring hyperacusis), and in report of discomfort to environmental sound (measuring phonophobia), in 182 individuals who received 12 months of TRT (the treatment group – TG) were measured. The prevalence of hyperacusis and phonophobia fell by 6.6% and 7.7% respectively, and mean LDLs increased significantly. Individuals who showed a greater change in tinnitus related reaction and perception experienced a greater change in LDLs, and reported fewer environmental sounds as being uncomfortably loud. Change in LDL was greater for those individuals who used noise generators.

Phonophobia was also measured in an unmatched group of 113 individuals who received no treatment for 12 months (the no treatment group – NTG). During this time the prevalence of phonophobia fell by 7.9%. However there was little change in numbers of individuals reporting sensitivity to specific environmental sounds, in comparison to the TG who showed a marked change. The prevalence of phonophobia was similar between the TG and the NTG groups at the start of the study period.

Methods

Two independent groups of individuals were selected:

- 186 individuals referred to the RNID MRU tinnitus clinic over a three year period, 182 of whom completed one year of treatment (*the treatment group-TG*);

- 113 individuals from the British Tinnitus Association (*the no-treatment group – NTG*).

The TG were stratified according to hearing status, and then randomly assigned to receive either:

- Directive counselling (DC) alone;
- DC plus just audible noise generators (DC + LLNG);
- DC plus noise generators at, or just below mixing point with tinnitus (DC + HLNG);
- DC plus hearing aids (DC + HA) (where hearing loss was present);
- DC plus combination instruments (DC + COMBI) (where hearing loss was present).

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Individuals received five sessions of TRT in a 12-month period. Baseline LDLs, and LDLs after each TRT session were measured with wide band noise. As there was no significant difference between left and right ears with respect to LDL, the amount of change in LDL or prevalence of hyperacusis, mean LDL for right and left ears combined was used in analyses. Individuals were classified as having hyperacusis if LDLs were less than 88.39dB SPL (for individuals with normal hearing) or 81.24dB SPL (for individuals with a hearing loss). These figures were based on data from Bentler and Pavlovic [5] on normal LDLs for pure tones, and for tonal complexes.

Phonophobia was measured by asking patients to indicate whether they found speech, music/TV, kitchen sounds, the vacuum cleaner or traffic sounds uncomfortably loud.

LDLs were not measured in the NTG, however phonophobia was measured in the same way as the TG at the start, and at the end of a 12-month period. The NTG received no treatment for their tinnitus during this time.

Results

Although individuals with hyperacusis as their main complaint were excluded, at the start of the study 20.9% (38/182) of the TG had hyperacusis. 35.2% (64/182) of the TG, and 33.6% (38/113) of the NTG reported sensitivity to at least one environmental sound.

Subjective report of discomfort to environmental sound was compared to objectively measured LDLs in the TG. LDLs exceeded the average intensity of the specific sound reported as being uncomfortably loud. The LDLs of individuals who complained of specific sounds as being uncomfortable were not significantly different from the rest of the TG. It was therefore possible that report of discomfort to specific environmental sound was more indicative of phonophobia than hyperacusis.

After 12 months of HBT the incidence of hyperacusis in the TG was significantly lower ($X^2 = 19.423$, $df = 1$, $p = <0.001$), and mean LDL increased significantly from 88.45dB to 93.17dB (MANOVA $f = 7.70$; $df = 4$; $p = <0.001$). However 14.3% (26) of the TG still experienced hyperacusis, and 27.5% (50) reported phonophobia. After 12 months the prevalence of phonophobia in the NTG was similar – 25.7% (29/113) of individuals still reported discomfort to one or more environmental sound. The reduction in number of individuals reporting phonophobia to specific sounds was greater in the TG than the NTG however.

Individuals who showed a greater mean change in questionnaire scales related to tinnitus reaction and perception experienced a greater reduction in LDL. This is shown in Figure 1. "Better" tinnitus was classified as a change of 40% or greater in 2 or more of the questionnaire scales loudness, annoyance, effect on life quality and percentage awareness.

"Same" was classified as a change in these scales of less than 40%, and "worse" was classified as an increase in these questionnaire scales. It is obvious that the change in LDLs was greatest for the "better" group.

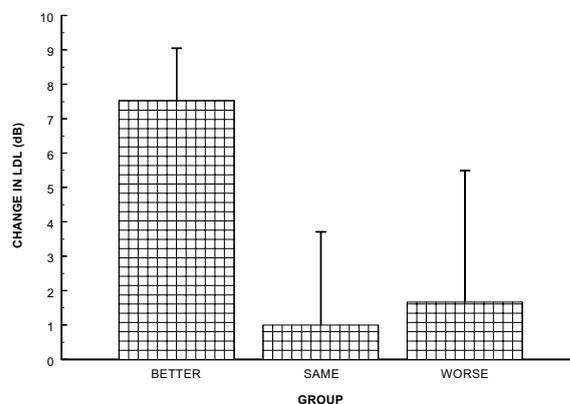


Figure 1 Mean change in LDLs after 12 months of TRT. Data are shown for individuals who responded to TRT (the "better" group, $n = 138$), individuals who did not change significantly (the "same" group, $n = 30$) and individuals whose tinnitus became worse (the "worse" group, $n = 14$).

There was also a tendency for individuals who experienced phonophobia at the end of the 12 month period to have responded less well to TRT than those who did not. This is shown in Figure 2.

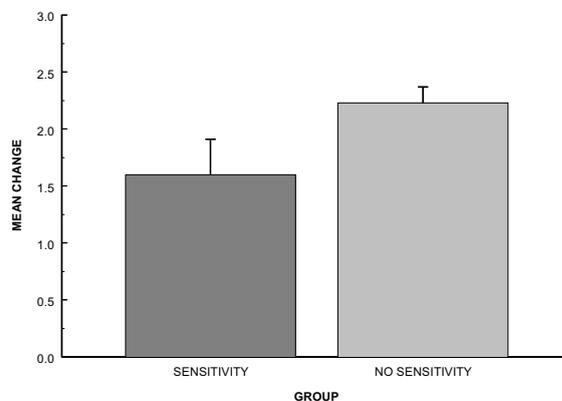


Figure 2 Mean change in questionnaire scales after 12 months of TRT for individuals who reported sensitivity to household sounds (vacuum cleaner, kitchen sounds, music/TV) after 12 months of TRT (*sensitivity*) ($n = 21$) and those who did not (*no sensitivity*) ($n = 161$).

Change in LDL was greater for those individuals who used noise generators in addition to directive counselling or amplification, even though noise generators were used at lower levels than would have been indicated for treatment of hyperacusis alone. The change in LDL appeared to be related to the device used, rather than differences in hearing status between the different groups. This is shown in Figure 3.

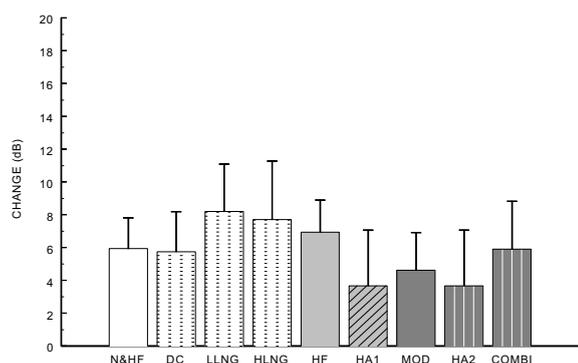


Figure 3 Changes in LDL after 12 months of TRT for individuals who received DC only ($n = 54$), DC + LLNG ($n = 36$), DC + HLNG ($n = 36$), DC + HA1 (individuals with mild high-frequency loss) ($n = 21$), DC + HA2 (individuals with moderate hearing loss), and DC + COMBI ($n = 13$). Change in LDLs for individuals with similar hearing status are shown separately from each treatment sub-group in solid colours so that differences related to hearing thresholds can be compared (*normal hearing and mild high-frequency loss = N&HF; mild high-frequency loss = HF; moderate loss = MOD*).

Conclusions

It appears that hyperacusis and phonophobia respond well to TRT, and that the amount of change in these factors is related to changes in tinnitus reaction and perception. This finding supports the theory that tinnitus and hyperacusis share a common mechanism. If this common mechanism is indeed increased central auditory sensitivity, then a reduction in sensitivity might lead to a lessening of tinnitus detection and corresponding changes in tinnitus perception and reaction.

Noise generators in addition to directive counselling or amplification appear to be most effective in reducing auditory sensitivity. This fits with the clinical experience that NGs are an effective treatment for hyperacusis.

The fact that the NTG showed little change in sensitivity to specific environmental sounds suggests that phonophobia is unlikely to resolve without treatment in individuals who are distressed by their tinnitus.

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Treatment history of incoming patients to the Tinnitus & Hyperacusis Centre in Frankfurt/Main

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The treatment outcome of Tinnitus Retraining Therapy (TRT) of patients who came to the Tinnitus & Hyperacusis Centre in Frankfurt/Main has been evaluated using questionnaires based on one proposed by Jastreboff. Out of 588 patients treated so far, 122 were selected whose treatment was considered to be concluded, since they were under the treatment for up to two years. The main factors used for assessing the treatment outcome were impact of tinnitus on the quality of life, tinnitus annoyance, severity, and loudness.

The characterization of the patients obtained during the initial interview will be presented to allow comparison of our population of patients with those reported by other centres, together with modification of recorded variables after the treatment. The treatment consistently reduced impact of tinnitus and/or hyperacusis on patients' lives, and resulted in decrease of tinnitus annoyance, severity, and subjectively perceived loudness. Individual cases will be presented as well.

Introduction

Patients at the Tinnitus & Hyperacusis Centre in Frankfurt/Main are regularly assessed by a questionnaire based on one proposed by Pawel J Jastreboff.

Method

From a total of 588 patients of the Centre, 122 were selected, whose treatment was considered to be

concluded, since they were under the treatment for up to two years. On the questionnaire tinnitus severity, annoyance, and impact on life are evaluated on a 10-point scale. Main criterium of improvement is the decreased impact of tinnitus on the quality of patient's life. Criteria of evaluation: Tinnitus severity, annoyance, and impact of life are decreased at least by 20%, more than one category has to be improved.

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Results

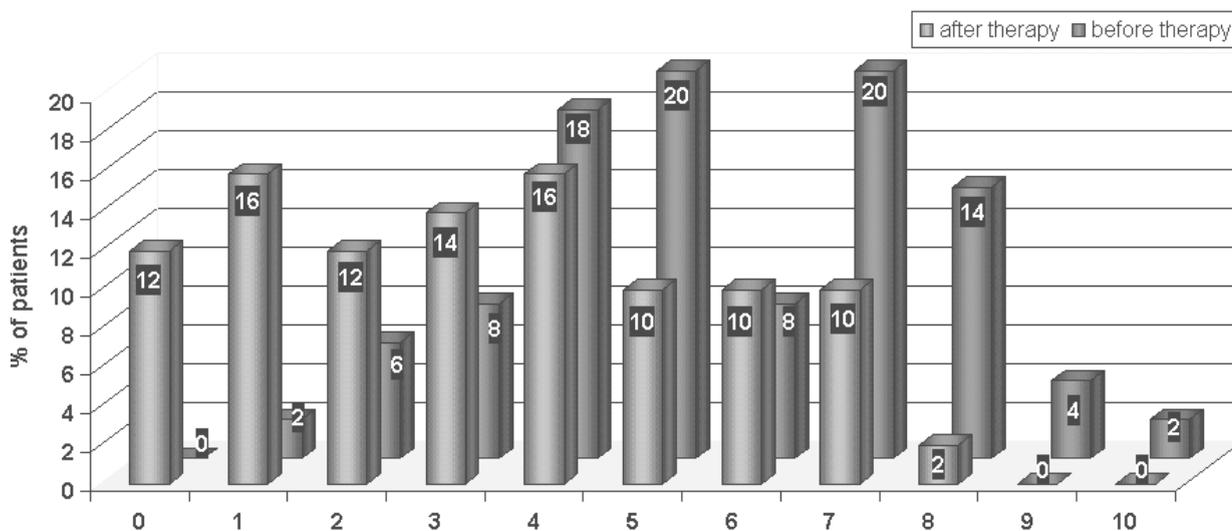


Figure 1 Impact of tinnitus on quality of life before and after TRT (n = 54)

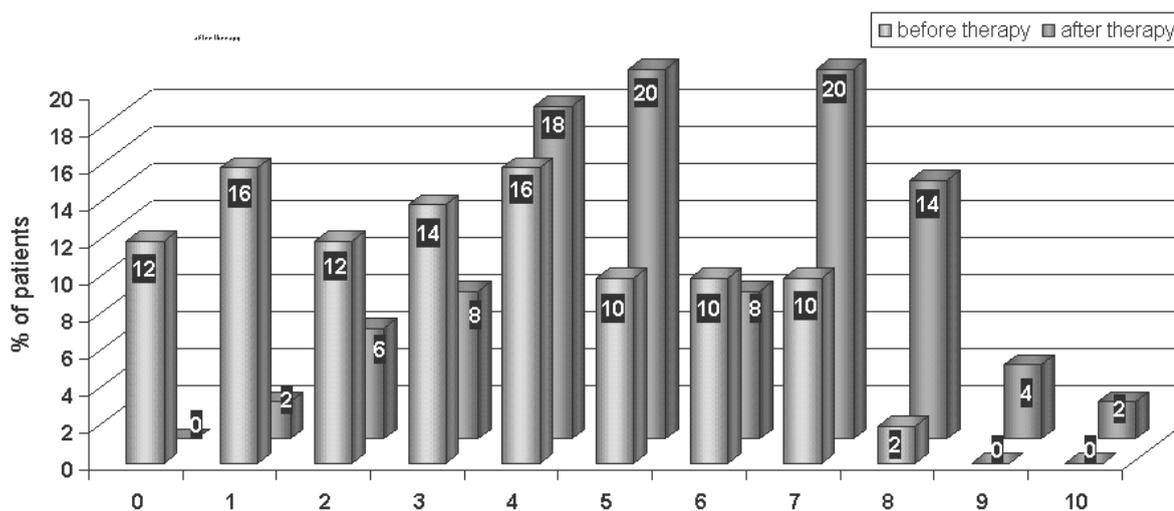


Figure 2 Tinnitus annoyance before/after TRT (n = 51)

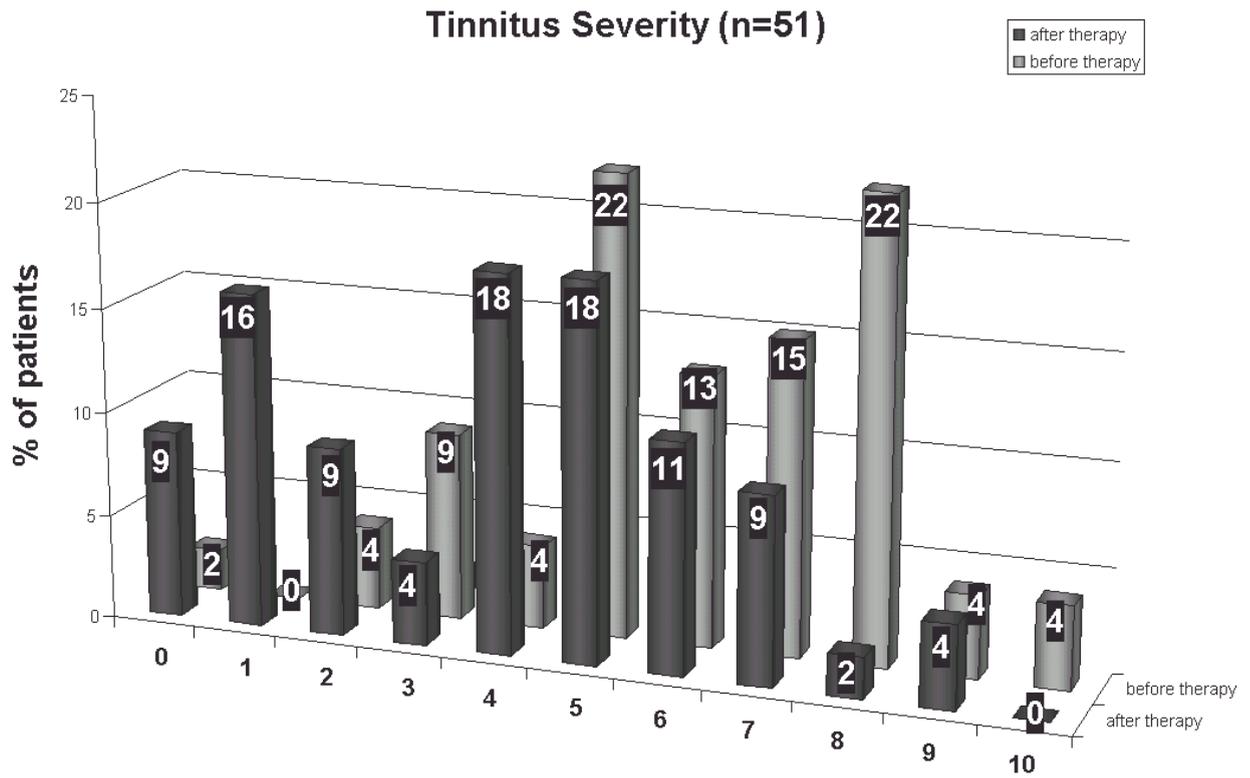


Figure 3 Tinnitus severity before/after TRT (n = 51)

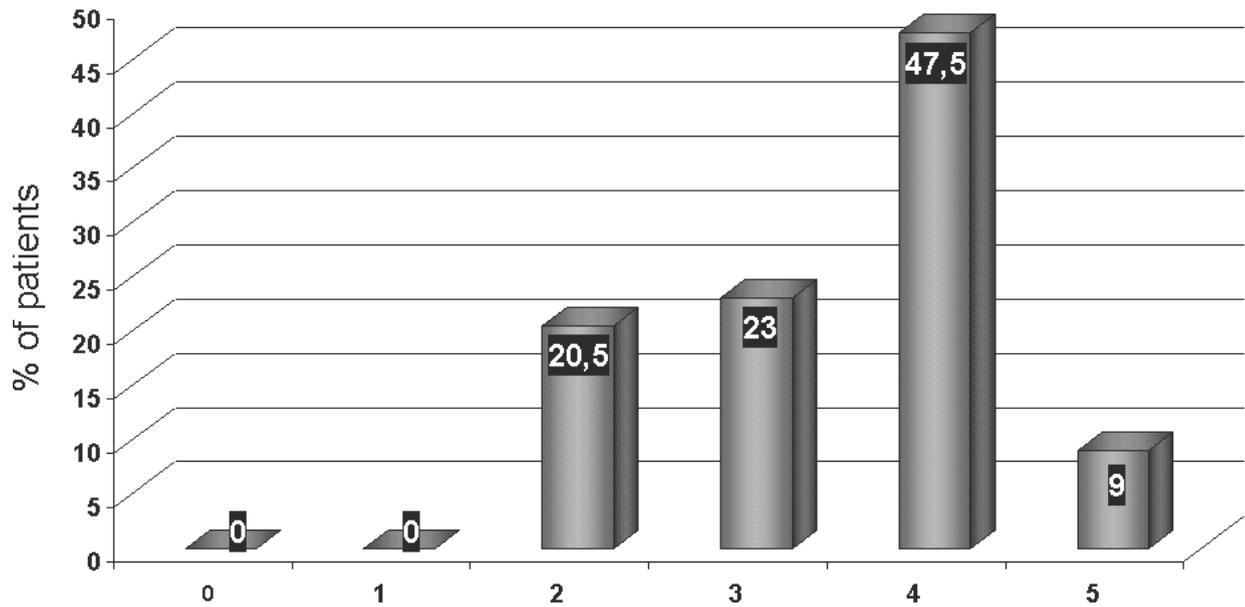


Figure 4 Tinnitus loudness before/after TRT (n = 122)

Therapy Outcome (n=85)

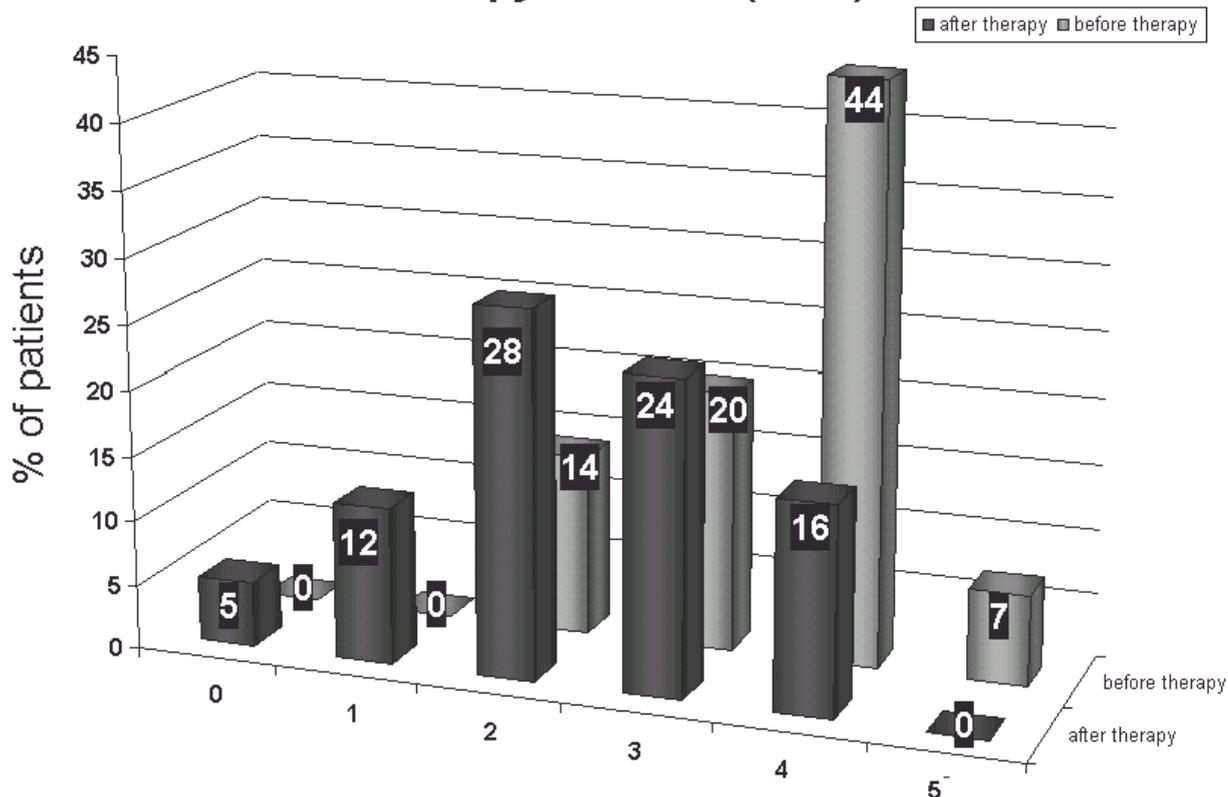


Figure 5 Therapy outcome of 85 patients (n = 85)

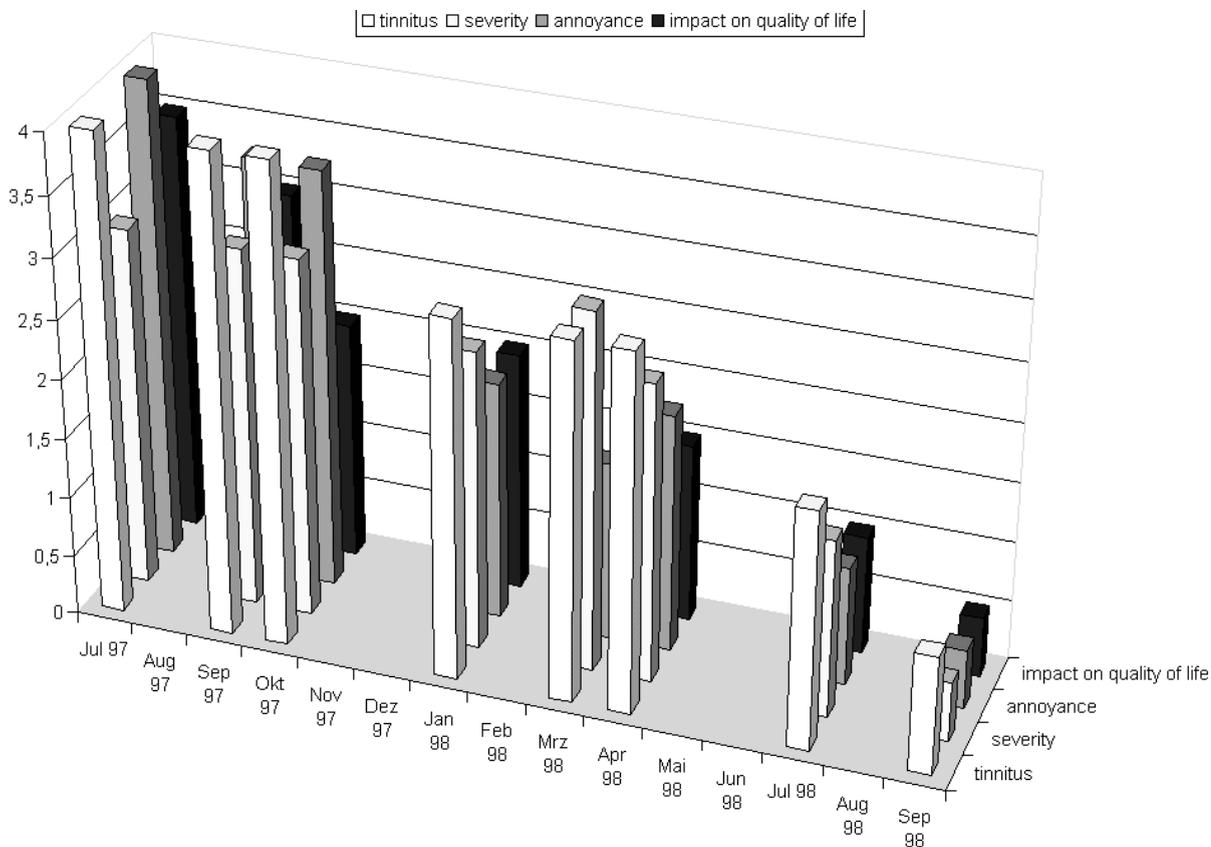


Figure 6 Therapy outcome of individual (Patient 21997074) case

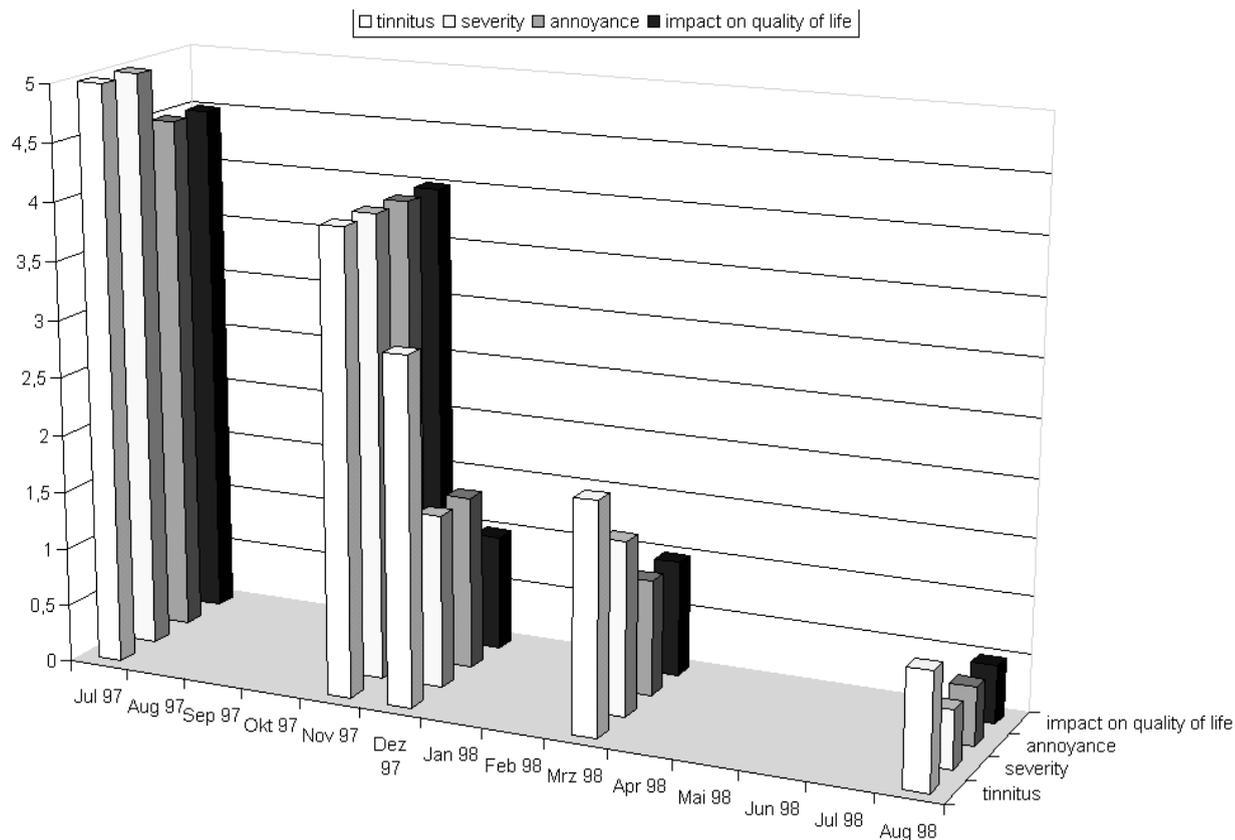


Figure 7 Therapy outcome of individual (Patient 21997083) case

Discussion and conclusion

The survey shows that a great majority of the patients of the Tinnitus & Hyperacusis Centre Frankfurt/Main show significant improvement.

TRT does not interfere with their individual life styles and the impact of tinnitus on their lives, tinnitus severity, annoyance, and loudness are consistently reduced.

Basic differences between directive counselling in TRT and cognitive strategies in psychotherapy: One illustrative case

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Directive Counselling in Tinnitus Retraining Therapy (TRT) and cognitive strategies in psychotherapy are complementary approaches to the problem of tinnitus. In those patients where a pathological emotional disturbance is blocking the action of TRT, the correct psychological treatment is essential, and positive results will be impossible until the pathologic emotional component is under control. Directive counselling in TRT acts by explaining to the patient what is happening and why it is happening within the auditory system, Psychological treatment acts by lowering the pathologic emotional associations to the tinnitus such as anxiety and depression, giving the patient techniques for emotional self-control and cognitive strategies to face the stress associated to tinnitus. The participation of a psychologist in the Tinnitus Clinic will improve the outcome of TRT, as patients with an uncontrolled pathological disturbance are clear candidates to failure.

Introduction

Among the patients in our Tinnitus Clinic on whom Tinnitus Retraining Therapy (TRT) is established, there are some that will require additional psychological help. These are patients affected by emotional disturbances that need specific treatment.

It is important to understand clearly the different and complementary roles of directive counselling, essential to TRT, and psychotherapy, as the combination of both approaches will be to the benefit of the patient.

We present an illustrative case.

Material and method

Case history

Sixty-five year old female, coming for the first time to our Clinic in June 1996, complaining of 4 months old pulsatile tinnitus in the left ear that varies with the position of the head. In the questionnaire (Sheldrake modified [1]) she rates the impact on life as 7/10, and annoyance as 10/10 in analogical scale. Her sleep is seriously affected. She shows evident signs of anxiety and depression.

Examination

Bilateral sensorineural hearing loss of 30 dB with drop in high frequencies. Pulsatile left low frequency tinnitus of 2 dB loudness. No other ENT findings. Duplex Echo-Doppler with no abnormal vascular findings.

Diagnostic

Pulsatile tinnitus and sensorineural hearing loss. Strong psychological component.

Treatment

TRT including directive counselling and bilateral sound generators. Specific follow-up program. The patient is sent to the psychologist of the Clinic for study and treatment.

Psychological study

In the interview the patient shows obsessive personality features (perfectionism, irresolution, excessively careful, minute and anticipated planning in all activities). Anxiety features (feelings of tension and apprehension, hypersensitivity to criticism and rejection, tendency to exaggerate possible risk or danger in daily life). Insomnia. Lack of concentration. Feelings of incompetence and insecurity. Reluctance, apathy, pessimism. Her main sources of stress are her own thoughts.

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Psychological test

Inventario de Situaciones y Respuestas de Ansiedad (ISRA) [2]. Results: Cognitive level; severe anxiety, 85/100. Physiologic and motor level; moderate anxiety.

Psychological diagnostic

ICD-10: mixed anxious and depressive disturbance F41.2 [3].

The patient was sent to the psychiatrist. The diagnosis was confirmed and Trazolone (ISRS) was prescribed as essential for the efficacy of psychotherapy.

Psychotherapy

Techniques of emotional self-control:

- Cognitive therapy [4], with the following rationale:
 - Thought – cognition – determine our mood.
 - Behind a depressed mood hide negative thoughts that give a fatal interpretation of the world.
 - Our negative thoughts are a consequence of a distorted cognitive focus.
- Assertivity training: The way of relating with others has become an important source of stress in life. Assertive acceptance refers to the ability of the individual to transmit warmth and express compliments or right opinion of others when their positive conduct justifies it [5].
- Relaxation training to lower anxiety with Jacobson techniques [81]. This technique is based on the rationale that our body responses to anxiety provoke thoughts and actions that imply muscular tension.

Results

Response to medication was positive. After 3 months of psychotherapy (12 sessions) the patient was able to realise the direct relation between stressing life events and worry and with it a higher perception of her tinnitus, and she was sent again to the otologist to follow TRT.

Sound therapy was now evaluated as acceptable and positive by the patient. Follow-up showed marked progressive improvement After 21 months the patient is not affected by her tinnitus anymore: and very often does not hear it. There are rare episodes of return of her pulsatile tinnitus but without emotional effects.

Discussion and conclusions

In our experience when a tinnitus patient has added psychic pathology we often find an

obsessive and anxious personality, frequently accompanied by depressed mood and/or depression and anxiety disturbances [7]. Being vulnerable to the different stressful situations generated mostly by their cognitive distortions, they generally will respond well to cognitive type psychotherapy [8].

In the case we present, Directive Counselling of TRT would not have been effective, as in our experience a psychological pathology that cannot be controlled by the specialist acts as a barrier that blocks the action of TRT.

Directive counselling in TRT acts by explaining to the patient what is happening and why it is happening within her auditory system [9].

Psychological treatment acts by lowering the pathologic emotional associations to the tinnitus such as anxiety and depression, giving the patient techniques for emotional self-control and cognitive strategies to face the stress associated to tinnitus.

For TRT to be effective any pathologic emotional component must be under control. Otherwise, the effect of both directive counselling and sound therapy will be delayed or limited.

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The importance of continuity in TRT patients: Results at 18 months

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We present the results in 56 patients that have accepted and followed Tinnitus Retraining Therapy (TRT) for 18 months. This group includes all patients seen in our Tinnitus Clinic for the first time between March 1996 and September 1997, when TRT was started. A follow-up plan was designed according to the needs of each patient. Those cases on which an emotional component could interfere with TRT were seen also by the psychologist of the group.

Of the 56 patients, 9 did not improve. Of these, 7 had required psychological or psychiatric help. In our experience TRT is effective in those patients who follow the treatment with perseverance and whose emotional component can be properly oriented by directive counselling or with the assistance of the psychologist. Patients with a strong emotional component that cannot be controlled even with the assistance of the psychologist or the psychiatrist are candidates to failure.

To impart TRT with success the doctor must be well trained in these techniques, and have a good command of the different factors involved in the emergence of tinnitus in each particular case. We must do our best to motivate the patient to overcome his scepticism or other possible difficulties, and to see the good results that his perseverance will obtain.

Introduction

Tinnitus is a symptom that will often lead the patient to seek medical help. In many cases, a good examination and audiological study to discard any retrocochlear pathology will be enough to tranquillise the patient, who will not pay attention to the symptom anymore. But we have experience that there is a group of patients where this medical action is not enough, and they complain of interference by the tinnitus in their quality of life. Traditionally they have been treated variously: with drugs [1,2], with physical procedures [3–6], with alternative medicine [7,8], or with surgery [9,10]. These procedures have not given enough satisfactory results, and very often the patient has felt frustrated and abandoned.

In fact, these varied approaches show that there has been no satisfactory treatment to help these patients. Very possibly the low success rate of these procedures is due to the fact that there are factors participating in the annoyance produced by the tinnitus that have not been considered in the therapeutic approach. Several authors have pointed in that direction, considering that there are central mechanisms implied in the persistence of the symptom [11] and that there are factors such as the attention and alertness mechanisms that play an important role in the perception of tinnitus [12].

For our ENT Department, the knowledge of the

neurophysiological model recognized by Jastreboff [13] and of the development of the Tinnitus Retraining Therapy (TRT) by Jastreboff and Hazell [14–20] and later other researchers [21–25] has opened new expectations for our patients. Its benefits are seen in the results obtained on those patients that comply carefully with the treatment.

Materials and method

The study includes all the patients seen for the first time in our Tinnitus Clinic between March 1996 and September 1997 who have followed the TRT treatment for 18 months or more (56). All these 56 patients referred to being annoyed by their tinnitus, that affected in different degrees their quality of life.

In all of them the diagnostic protocol followed the same pattern:

- Specific tinnitus history including its acoustic characteristics, its possible triggering cause, its interference in daily life, family and social factors that could be related to the annoyance; possible systemic diseases; previous treatments followed for the tinnitus; previous advice or opinions received in other clinics or support centres.
- Full ENT examination.
- Audiologic study: pure tone audiometry, speech audiometry, BERA, tinnitus measurement that included frequency matching by closed choice, loudness match, minimum masking level and residual inhibition.

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- All responded to a questionnaire (Sheldrake modified [26]) where the patient was assisted to self-evaluate: the loudness of his tinnitus and its annoying effect on his life on analogical scaling; the number of hours the tinnitus is perceived; the family and social difficulties it produced; beliefs and possible fears of the patient.

For all the 56 patients after being diagnosed TRT was established: directive counselling and sound therapy (avoid silence and use of sound generators or hearing aids if needed) were adapted to the needs of each case. 23 patients (41%) required psychological help (relaxation techniques and other therapies) alone or with additional psychiatric treatment. A follow-up plan was established for each patient depending on the particular needs and circumstances.

The evaluation of the progress of each patient was done through the clinical history, together with the evaluation questionnaire where the patient evaluated his progress through the analogical scales previously described and the social and family impact.

Results

After 18 months of treatment with TRT, 47 patients (84%) have greatly improved, and for 34 of them (61%) the tinnitus is not a problem anymore and often is not heard. 9 patients (16%) did not feel any improvement. Of these, 7 (12%) presented a psychological component that could not be controlled, 1 patient (2%) presented an active endolymphatic hydrops with dizziness, fluctuating hearing loss and very variable tinnitus, and 1 patient (2%) did not see his tinnitus disappear as he wished, although from the first examination he had indicated that he did not feel annoyed by it.

Discussion and conclusions

The results obtained with TRT in this group indicate its effectiveness in those patients that follow the treatment to the end.

Nevertheless there is a group of patients in which the strong psychological component that cannot be controlled by the specialist acts as a barrier that blocks the action of TRT.

For the patient with active endolymphatic hydrops the fluctuation in his hearing, the dizziness and the changes in the tinnitus made habituation very difficult. Anyhow, there is another patient with hydrops in the group with the best evolution.

The patient with no annoyance who wanted his tinnitus to disappear should never have started TRT, as the purpose of this technique is to eliminate the impact of the tinnitus in life.

There is another large group of patients that attended the tinnitus clinic and that either did not accept the treatment or abandoned after one or two visits. In the period of time we are studying, 188 patients were seen in the Tinnitus Clinic, but only

56 (30%) complied with the treatment and were followed for at least 18 months. Of the remaining 132 (60%) patients we have been unable to do a proper study of their reasons, as the investigations carried out did not give enough valid information. We know that for some patients the full examination of their tinnitus and the counselling given in the first visit was sufficient to know that their tinnitus did not have any meaning and they felt that nothing more was required. Others might have been sceptical of the treatment, or considered that 18 months for full results was too long. Of this group we could presume that maybe their tinnitus was not a real problem and they did not see the need for such long treatment, or maybe they felt it would be too expensive or difficult.

It is interesting to note that of the tinnitus patients seen in our Clinic that were members of associations of tinnitus sufferers, only 1 followed the treatment to the end, with good results.

Another possible explanation is that, although we started TRT in 1994, the Tinnitus Clinic was not established as such until the beginning of 1996. This group of patients were seen shortly after, and maybe we were not yet sufficiently fluent or convincing in the implementation of TRT. It is important that the doctor imparting the directive counselling and evaluating the factors that contribute to the tinnitus being a problem, will have a thorough knowledge of TRT, and be able to adapt it to the particular needs of each patient and answer his questions. The patient must be convinced that the neurophysiological model explains his particular case and that the treatment proposed is what he needs, so that he is encouraged to follow the indications given and comply with the follow-up program.

Whatever the reasons for not following the treatment, we have seen in these results that TRT is the therapeutic tool we needed for those patients in whom the tinnitus is a real problem, as it offers a high percentage of improvement that will give back to the patient its quality of life.

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The effects of managing hyperacusis with maskers (noise generators)

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The study addresses the effects of using maskers in the ambulatory treatment of hyperacusis. 23 patients (12 male, 11 female, mean age 52.6 years, $s = 13.6$ years), with and without hearing loss, stating a threshold of discomfort for sounds in the range of 500–4000 Hz, at 82 dB, in pure-tone audiogram and a dynamic range of 63 dB were fitted with softmaskers within a tinnitus retraining therapy. Audiometric measurements: uncomfortable loudness level (ULL) and the dynamic range were done at the beginning of the intervention, 3, 6 and 9 months later. The tinnitus questionnaire after Goebel and Hiller and visual analogue scales after Jastreboff were also used. A substantial decrease in the uncomfortable loudness level (ULL) and a corresponding increase of the dynamic range was found. In the subjective data much more acceptance of ambient noise and an improved well-being was expressed as the treatment proceeded.

Hyperacusis is an often overlooked secondary phenomenon of tinnitus which is generally perceived as being more problematic than the tinnitus. Of the patients undergoing the two-year Tinnitus Retraining Therapy at the Osnabrueck Hyperacusis Center, 23 patients had already completed nine months of the retraining programme at the time of data collection. All the patients suffer both from tinnitus and hyperacusis, hyperacusis presenting the main problem.

Hyperacusis is defined as an abnormal, generally painful perception of loudness in relation to all normal external noise [1]. The limits of uncomfortable loudness level (ULL) tolerance measured in the pure tone audiogram lie <100 dB, which suggests an increase in amplification in the hearing channels following diminished auditory function. The dynamic range is considerably limited over the entire frequency range. Hyperacusis is to be distinguished from recruitment [1], which is generally associated with sensorineural hearing impairment (reduction of the hair cells). Here the dynamic range is limited due to the changes of the neural elements [2].

Methods

Twenty-three patients, age 20 to 78 years ($\bar{x} = 52.6$ years, $s = 13.6$ years), took part in the study (see Table 1 for gender distribution and family status). 61% of the patients had light to medium hearing loss (audiometric data, see Table 2). The data collection considered the frequency range between 500 and 4000 Hz.

The pure tone audiogram measured an uncomfor-

Table 1 Gender distribution and family status of the Patients

| | male | female |
|-----------------------------|------|--------|
| Number of patients (n = 23) | 56% | 44% |
| Married | 72% | 43% |
| Never married | 11% | 29% |

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Table 2 Audiometric data

| | |
|-------------------------------------|-----|
| High frequency loss | 58% |
| Broad band hearing loss | 3% |
| Normacusis | 39% |
| Tinnitus loudness ≤ 5 dB dB/SL | 84% |

table loudness level (ULL) for tones of an average of 82 dB and a mean dynamic range of 63 dB. All patients were fitted with maskers within the Tinnitus Retraining Therapy after receiving a comprehensive briefing on the method of operation and use of the equipment. The retraining commenced with the volume of the maskers set at the hearing threshold. In regular follow-up appointments of approximately 4 weeks the volume was increased to the mixing point [3].

Data collection was done by means of audiometric readings (changes to the ULL and dynamic range) taken at the beginning of the intervention and after 3, 6 and 9 months after fitting of the maskers. All patients were categorized using the Jastreboff method (Baltimore questionnaire [4]),

severity of the tinnitus, hyperacusis and hearing difficulty being rated on a six-level visual analogue scale (level 0 = no problem, level 5 = big problem). Only patients that rated hyperacusis as the biggest problem were included in the study. To get subjective rating also the tinnitus questionnaire (TF) [5] and the six-level visual analogue scale (level 0 = ear sounds, no problem, level 5 = ear sounds worse) after Jastreboff [4] were used.

Results

Regular wearing of the maskers led to an average shifting of the uncomfortable loudness level from 82 dB to 103 dB (Figure 1) and a corresponding extension in the dynamic range from 63 dB to 90 dB on average (Figure 2). On the Jastreboff analogue scale the values improved from an initial 4.5 (= hyperacusis is a big problem) to 0 (= hyperacusis no longer is a problem) (Figure 3). In tinnitus questionnaires (TF) completed 6 and 12 months after the beginning of treatment, the problem score improved from 52 to 28 (Figure 4), which, according to Goebel and Hiller [5], indicates that the tinnitus, which was initially complexly decompensated, had become a compensated tinnitus.

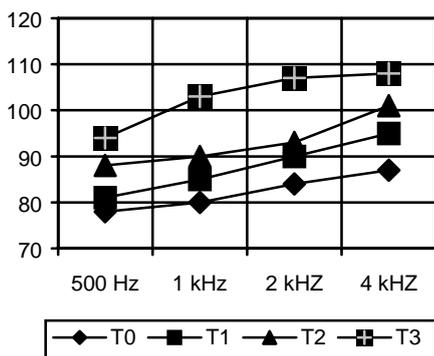


Figure 1 Changes in uncomfortable loudness level ULL (T0 = beginning, T1 = after 3 months, T2 = after 6 months, T3 = after 9 months) (n = 23)

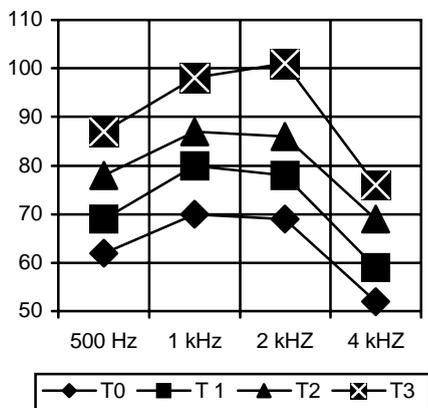


Figure 2 Changes in dynamic range (T0 = beginning of the intervention, T1 = after 3 months, T2 = after 6 months, T3 = after 9 months) (n = 23)

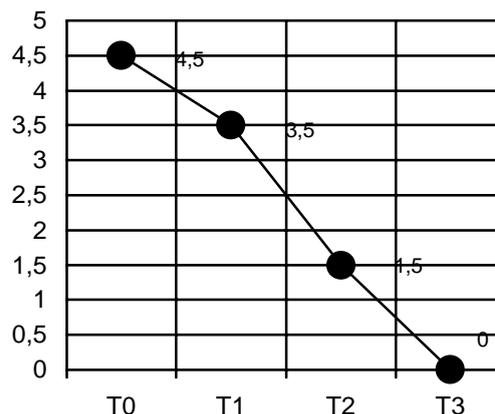


Figure 3 Subjectively rated severity of hyperacusis (Baltimore Questionnaire after Jastreboff) (0 = no problem, 5 = worse) (n = 23)

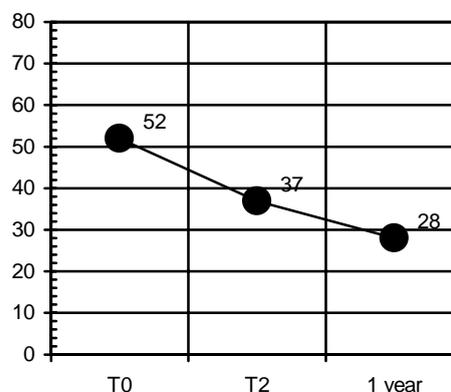


Figure 4 Subjectively rated impairment caused by tinnitus. Tinnitus questionnaire after Goebel and Hiller. (Possible range of values from 0 to 84 points) (n = 23)

Discussion and conclusions

The aim of the study was to examine the effectiveness of regularly using maskers for several hours in the treatment of hyperacusis and tinnitus. It emerged that exposure to noise generators caused a resetting of the incorrectly programmed neuronal structures. This manifested itself particularly clearly in the improved acceptance of ambient noise. In all the indices used in the study to record the experience of and impairment caused by hyperacusis and tinnitus, a substantial improvement in the patient's well-being and experience of changes to the hearing range were observed.

It is planned to continue the measurements over a period of 15 months in order to document the stability of the improvements achieved. In addition, long-term catamnestic studies would seem desirable.

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Tinnitus interaction with auditory threshold using different sound envelopes

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We speculated that tinnitus might interfere more with the near threshold detection of continuous sounds than with that of beeps consisting of only a rise and a fall phase. To test this, a computer version of the Von Békésy audiograph was implemented, using the Direct-X technology, which allows modulating by a user-specified envelope a sinusoidal sound that slowly shifts in frequency. The amplifier gain is continuously decreased or increased, depending on whether a key, indicating that the sound is heard, is pressed or not. Threshold is estimated as the series of midpoints between key presses and releases. The present study represents an initial exploration of this tool with three subjects having a tinnitus, to assess if the speculation appears viable and worth more investment. We limit this brief report to the comparison of thresholds to a continuous tone (modulated only by the gain control associated with the response key) and to a 20 ms beep (10 ms rise/fall time) presented every 200 ms. The threshold curves directly reflect the amplifier gain, without compensation for the 14.2 dB loss in energy associated with the envelope forming the beep. In two subjects (A, bilateral tinnitus, and C, right ear tinnitus), the tinnitus was successively matched to widely varying pure tones in the 1 to 5 kHz range, while subject B's tinnitus (left ear) could only be assessed as above 6 kHz. Both A and B showed crossing threshold curves: the continuous sound was detected at lower gain than the beep for low carrier frequencies (below 1.5 kHz or so) but the beeps were better detected at higher frequencies (mostly 3–4 to 8–10 kHz). Subject C did not show thresholds for the beeps at lower gains that for the continuous tone but, at a slow sweeping rate providing more detailed threshold curves, the continuous tone threshold raised to the level of the beeps threshold, for each ear separately, during a significant interval near 4 kHz. Control subjects are still required to go beyond speculation in relating the observed interactions to tinnitus. This exploratory study provides enough support to warrant an extensive formal study of the relationship of tinnitus with the auditory threshold to sound modulated by different envelopes.

Introduction

The present unsubsidized exploratory work is that of beginners in the fields of audiology and tinnitus. Its main merit might be a fresh, although perhaps naive, look at the problem of providing an objective indicator of tinnitus. Our earlier work concerned a possible event-related potential (ERP) indicator of pure tone tinnitus. The research strategy was to identify stimulating conditions with three tones such that, without tinnitus, the similarity of the ERP to the middle tone with the other two ERPs would be larger than the similarity between these two ERPs (evoked by tones at frequencies further apart). Our speculation was that the specific pro-

cessing of a tone close to a continuous tinnitus should be selectively modified. In particular, if the middle frequency matches the tinnitus, its ERP might lose similarity with the other two ERPs, leading to the latter being more similar between themselves than with the ERP to the middle tone. We focused mainly on steady-state ERPs until we realized that our stimuli, consisting of a rise and a fall phase with no plateau, addressed essentially the transient responses, while the ongoing cerebral activity corresponding to the tinnitus and susceptible to interfere selectively with the processing of external stimuli is essentially of the sustained type.

Turning our attention to psychophysics, we could not find studies contrasting thresholds obtained with different rise/fall and plateau duration. Adapting our ERP strategy, we expected that, in the vicinity of the tinnitus pitch, the sustained brain activity corresponding to the tinnitus should interfere with

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stimulus detection (raise its threshold) more for continuous tones than for beeps consisting only of onset and offset phases. We now report initial observations of threshold curves for continuous tones and beeps in tinnitus subjects.

Methods

A computer version of the Von Békésy audiograph was implemented using the Microsoft Direct-X technology in conjunction with standard PC audio board and game pad. The program, called Liminal, establishes auditory threshold by providing a sinusoidal sound wave that ramps in frequency (default: 1 octave/minute (O/m); default limits: 0.1 and 20 kHz, backward sweeping permitted). The amplifier gain is updated (default: 2.5 dB/s) at very short intervals; it decreases while a game pad button is pressed, indicating that the sound is currently audible, and it increases otherwise. A repeating envelope is also applied to the frequency sweeping sinusoidal sound (default: a rectangular envelope not modifying its input). Each envelope is defined by six parameters: the minimum (valley) and maximum (plateau) amplitudes, and the duration of the rise, plateau, fall and valley phases. Rise and fall have the shape of a half cosine. Thus, a 20 ms beep with 200 ms SOA is specified by parameters (0, 1; 10, 0, 10, 180), meaning that maximum amplitude is full (1), rise time is 10 ms, there is no plateau phase (duration of 0 ms), fall time is also 10 ms and the valley, at intensity 0, provides for an ISI of 180 ms, making this envelope repeat every 200 ms. Liminal displays the session's progress and archives the frequencies and amplitudes at which the key presses and releases are detected. Continuous threshold is established as the line joining the mid points of consecutive response key events.

A separate mode allows the subject to control the frequency and intensity of the sound, using the eight-direction "joystick" button of the game pad, to define a sound that subjectively matches the tinnitus.

We report on three subjects with tinnitus. Subject A is a male in his 30's; his tinnitus installed gradually over years and is felt at both ears. Although he reported very satisfactory matches to his tinnitus, successive evaluations from different starting points yielded disparate evaluations (e.g. near 2.0 kHz, then near 3.2 kHz). Subject B is a male in his 60's with a left ear tinnitus of unknown history with a pitch above 6 kHz, in a part of the spectrum where his frequency discrimination is very poor. Subject C is a female in her 50's, with a right ear tonal tinnitus whose onset reportedly followed auditory brainstem potential testing with clicks up to 100 dB SPL. Her tinnitus matches varied in the 1–5 kHz range.

These subjects were respectively tested on three, one and two occasions with this software (first session data lost for C). Subject A reported each time that the sounds exacerbated his tinnitus. The third time, that was still felt one week later. Subject B's tinnitus was not affected by the sounds presented,

while Subject C experienced both exacerbation and temporary annihilation of her tinnitus. Fast modulation (envelope: 0, 1; 10, 0, 10, 0) was exacerbating while the same 20 ms beeps spaced every 200 ms tended to pacify her tinnitus. The matching procedure, using a newly specified long envelope (0, 1; 100, 3500, 100, 300), regularly caused her tinnitus to vanish for a duration of the order of the minute, which made matching more difficult. During the threshold sessions, she tried to signal when the sweeping frequency was close to her tinnitus if present.

Although different sound envelopes were explored, we restrict this report to the comparison of thresholds for a continuous sound (default doing nothing envelope) and for 20 ms beeps every 200 ms (envelope described above). The effect of this envelope is to reduce the sound energy by 14.2 dB. The results are reported in terms of the amplifier gain, without adjustment for the envelope effect nor for the frequency response of the commercial earphones used.

Results

The stimuli were presented bilaterally to Subject A. His first session showed that below about 0.6 kHz the beeps required some 8 dB larger amplification that the continuous sound to be perceived, but they became better detected than the continuous sound, particularly above 3 kHz. The slower sweeping rate of the second session provided more detailed curves that reproduced the beep advantage from 3.3 kHz to the 3.6 kHz testing limit. The third session, about four months later, involved backward sweeping from 6 to 2 kHz at both 1 and 0.2 O/m. No crossing

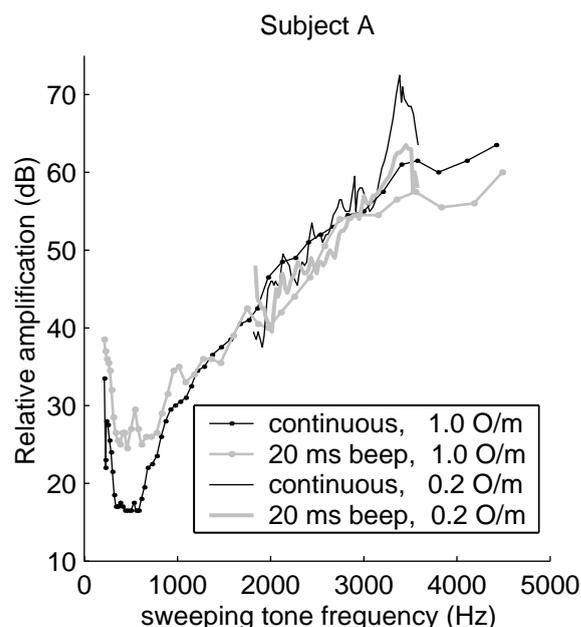


Figure 1 Subject A was tested for 0.1 to 5 kHz sweeping at 1 O/m (dotted lines) and, about one week later, for 1.8 to 3.6 kHz at 0.2 O/m (plain lines).

but a nearly constant 8 dB advantage of the beep over the continuous sound was seen throughout the range tested.

A crossing pattern was also seen in Subject B at both ears separately, wherein the beeps required larger amplification than the continuous sound below about 1.5 kHz but smaller amplification, at least from 5 to 8 kHz.

Subject C (second session) never showed detection of the beep at lower amplification than the continuous sound. In sweeping from 0.1 to 8 kHz at 1 O/m, the difference was about 10 dB at the right ear, but reduced to about 4 dB from 1 to 3.5 kHz, and it was about 12 dB at the left ear, reducing to about 8 dB from 1.5 to 4 kHz or so. Sweeping more slowly (0.2 O/m) from 6 to 2 kHz showed, at the right ear, a 6 to 14 dB difference, except for very near curves from 3.8 to 4.2 kHz (the continuous tone raised to the level of the beep); a similar pattern was seen at the left ear, except that the two curves are nearly superimposed from about 3.3 to 4.3 kHz.

Discussion and conclusion.

The data show many instances where the advantage of the continuous tone over the beep having 14.2 dB less energy was reduced, even inverted, in a frequency range where the tinnitus could be located. This is consistent with our expectation that tinnitus could interfere more with the perception of continuous or slowly rising sounds than with that of sounds having fast rise and fall and no plateau. For monaural tinnitus, the effect was not specific to the affected ear, which is consistent with a central origin.

The main lack of the present study is control subjects with no tinnitus. Without them, the link to tinnitus is only speculative. Reliability is also uncertain, because this exploratory study never implemented a within subject replication using the very same parameters. Nevertheless, our limited objective is achieved: this preliminary evidence justifies pursuing the present approach in a systematic, scientific fashion.

The effect of the bandwidth on the quality of the tinnitus-masking sounds

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The aim of the present study was to increase the pleasantness and the acceptability of custom-made masking sounds by changing the bandwidth of the noise centered about tinnitus frequency. This study covered 219 tinnitus patients. Noises with the bandwidths of 25, 50, 100, 250, 500, 1000, 2000 Hz were generated for every patient. The center frequency of each narrow-band noise was the pitch-match frequency of each patient's tinnitus. The masking sounds and the white noise were presented to the patients at the minimum masking levels and patients were asked to choose the more pleasant and acceptable one. A noise with a bandwidth of 1000 Hz or less was preferred by 85.8% and a noise with a bandwidth of 250 Hz or less was preferred by 57.5% of 219 tinnitus patients. 80.8% of patients found noises with a bandwidth of 2000 Hz and the white noise to be irritating. The bandwidth of a masking noise seems to be a parameter that determines the pleasantness of the masking noise and plays a significant role for acceptability of the masking sound by the patients.

Patients and methods

We studied 219 patients who had primary complaint of subjective severe tinnitus and accepted the masking therapy using custom-made noise recorded on cassette tapes. 140 (63.9%) out of 219 patients were male. Age ranged from 22 to 77 years (mean age: 52 yrs). Duration of severe tinnitus ranged from one to 18 years (mean 6 yrs). 16 (7.3%) patients had no hearing loss in the 125–8000 Hz frequency band.

Patient-specific masking noises were generated using a system consisted of an IBM (compatible) personal computer equipped with a 16-bit soundboard, a tape recorder, and special software. In the system, white noise (random noise with flat frequency spectrum) was generated using the mathematical software tool MATLAB and the PC. Narrow-band noises were generated by passing white noise through a finite impulse response digital filter. A Chebychev type window function was chosen due to its sharp response in the transient band and small ripples in the stop band of the resulting filter. The order of the filter was 200 and the ripple level is –90 dB. In the present implementation, the sampling rate was 32,000 Hz, and sample quantisation was 16 bits. The signal synthesised within the PC was repeated in a loop, and it was played through the sound blaster card. Noises with the bandwidths of 25, 50, 100, 250, 500, 1000,

2000 Hz were generated for every patient. The center frequency of each narrow-band noise was the pitch-match frequency of each patient's tinnitus. When pitch match was less than 1000 Hz, only the noises with possible bandwidth were generated.

Minimum masking level for each noise was determined and two noises with minimum and maximum bandwidths were presented to the patients at the minimum masking levels for five seconds successively. Patients were asked to choose one that was more pleasant and acceptable, between the two sounds. The unselected one was dropped out. The procedure was continued and the finally selected narrow band noise was compared with the white noise. The procedure was repeated until the patient had a clear choice. The preferred noise was recorded on a cassette tape. The patient could listen to the sound using a Walkman cassette player whenever needed.

Results

A noise with a bandwidth of 1000 Hz or less was preferred by 85.8% and a noise with a bandwidth of 250 Hz or less was preferred by 57.5% of 219 tinnitus patients. 65.7% of tinnitus patients found slight or very slight differences among sounds with the bandwidths of 25 to 250 Hz. Others heard no difference. 80.8% of patients reported that the masking noises with a bandwidth of 2000 Hz and the white noise caused some irritating acoustic perception. Bandwidth preferences and pitch-match frequencies of tinnitus patients are presented in Figures 1 and 2.

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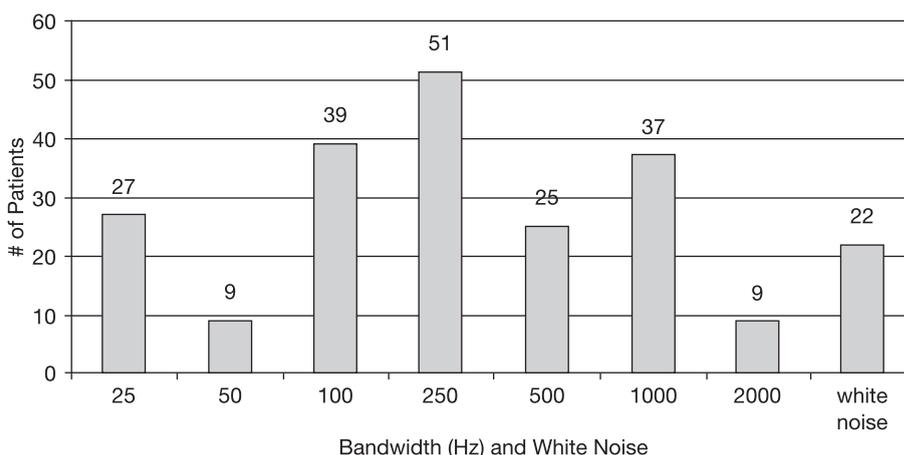


Figure 1 The bandwidth preference of 219 tinnitus patients.

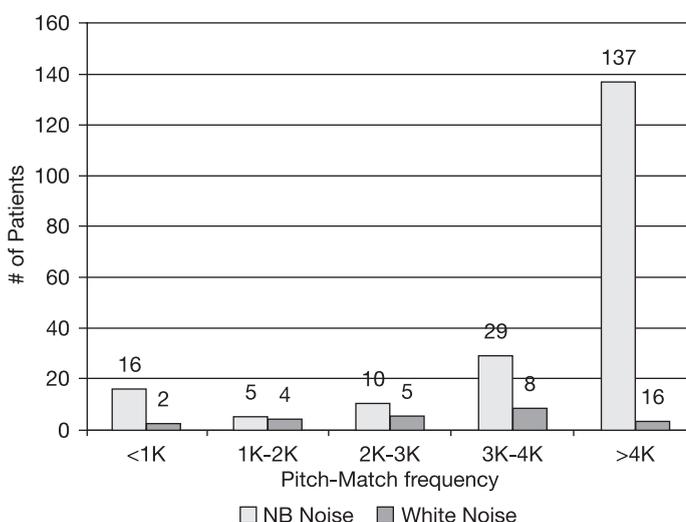


Figure 2 Patients preferring narrow-band noise vs white noise.

Discussion

In acoustical masking therapy, it is a prerequisite for the masking sounds to be acceptable to the tinnitus patient [1]. To increase the pleasantness of a masking noise will probably enhance the acceptability of the masking noise and consequently the effectiveness of the masking therapy.

The present study shows that the bandwidth of a masking noise seems to be one of the parameters that affects the pleasantness of the preferred masking noise. The study finds out that the narrow band masking noises with bandwidths in between 100 Hz and 1000 Hz are more preferable masking sounds and they can be used in masking therapy without causing any irritating perception of the white noise. However, some patients found the white noise and the noise with a bandwidth of 2000 Hz more acceptable. This leads that there are some other factors affecting the pleasantness of masking sounds for some tinnitus patients. One of the factors may be the bandwidth of the patient’s tinnitus itself.

Patients having tinnitus like a sound with large bandwidth may find that the most effective masking sound is the white noise or the masking sound with large enough bandwidth obtained from a sound reproduction system. The other factors may be the education of the patient and his/her aesthetic preferences. The points are some of the open questions in the subject.

It is possible to conclude from the results of the present study that most of tinnitus patients prefer the narrow band masking noise compared with the white noise. Therefore it is worth to tailor the center frequency and the bandwidth of masking noise for the majority of tinnitus patients.

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Fully-automated system for tinnitus loudness and pitch matching

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Ongoing work in this laboratory is addressing the need to develop standardized methodology for clinical quantification of the acoustical sensations of tinnitus. Because automation can be an effective means to achieve standardization, instrumentation and procedures have been developed to perform automated tinnitus testing. The testing hardware consists of a main computer, subject computer and audio instrumentation located in the testing room, and a "touch-sensitive" computer monitor located in the sound booth. A custom-programmed software application enables automated evaluation of hearing thresholds, and tinnitus loudness and pitch matches. The patient receives instructions via text displayed on the touch screen, and fingertip-touches the screen to make response choices.

Introduction

At the 5th International Tinnitus Seminar in 1995, we introduced a prototype system for conducting computer-automated matching of tinnitus loudness and pitch [1]. We noted the need for standardized protocols for quantification of tinnitus sensations, and pursued the reasoning that automated testing could effectively achieve standardization. Results of testing with the pilot system demonstrated that hearing thresholds and tinnitus loudness matches could be obtained reliably. Subsequently, the system was further developed and has been used in a series of studies designed to determine the most effective methods for obtaining hearing thresholds, and tinnitus loudness and pitch matches. Methodology for obtaining reliable thresholds and loudness matches has been documented [2], and current efforts focus on obtaining reliable pitch matches. Our goal is to develop a battery of automated techniques to quantify the various perceptual attributes of tinnitus. The present report briefly describes the automated tinnitus testing system with regard to hardware, software, and its measurement capabilities.

Methods

Hardware. The three major hardware components of the automated tinnitus testing system

include (see Figure 1): (1) the main computer (Dell Dimension 166 MHz Pentium CPU); (2) a custom-built signal conditioning module for signal generation, mixing, attenuation, and headphone buffering (Programmable Auditory Laboratory, aka PAL3000); and (3) the subject computer with touch-sensitive monitor (Dell Optiplex Pro, 200MHz Pentium Pro CPU with Microtouch 15" capacitive touch LCD display). The system can also be configured with portable notebook style computers if necessary for portability or space conservation.

Acoustic subsystem. The acoustic subsystem consists of the signal generation and conditioning module (PAL3000) and insert earphone transducers (Etymotic Corp. ER-4). The PAL3000 (Programmable Audio Lab 3000) instrument was designed and developed specifically for use in audiometric research by engineers at the Veterans Affairs (VA) National Center for Rehabilitative Auditory Research (NCRAR) located at the Portland VA Medical Center, Portland, Oregon, USA. The PAL3000 provides pure tone generation, audio signal conditioning, switching, mixing, attenuation, and power buffering. The instrument is controlled through the use of a standard computer serial port.

Subject instruction and response subsystem. The main computer and the subject computer are connected via a local area network (LAN) interface using standard networking protocols for two-way communication. The subject instruction and Response subsystem is used to display prompts, messages, and instructions on the subject computer (touch screen), and to relay subject test responses back to the main computer.

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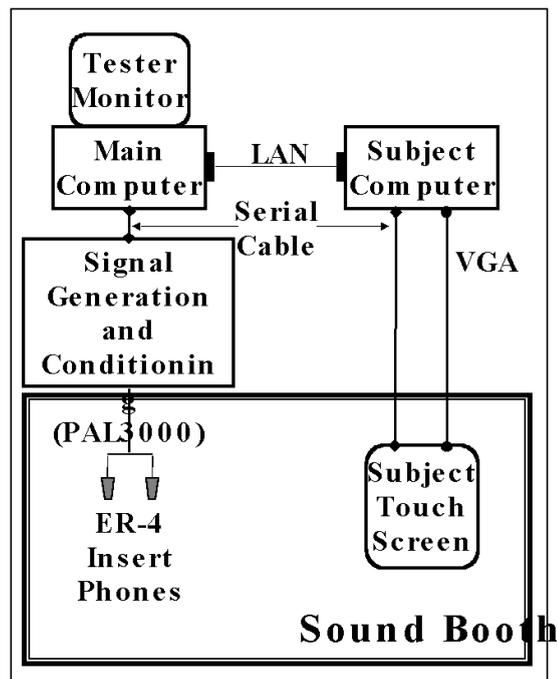


Figure 1 Block diagram of hardware used for computer-automated tinnitus evaluation.

LAN = Local Area Network. VGA = Video Graphics Array.

System calibration. A computer-controlled automated calibration routine was developed with serial interface control of a B&K 2231 sound level meter and Type 1625 octave filter set. The ER-4 insert earphones are coupled to the sound level meter using a B&K Type 4157 ear simulator. The calibration application generates a multi-frequency, multi-level calibration factor set. The calibration values are stored in a database and later accessed while testing to provide attenuation settings for calibrated sound pressure stimulus levels.

Software. Both the main and subject computers use the Microsoft Windows 95 operating system. All software was designed to be Microsoft Windows 95 compatible. Microsoft Windows OLE remote automation technology provides the virtual connection between the main computer and the subject computer at the application level for passing control, instruction, and response messages.

Software was developed to simultaneously control: (1) temporal parameters of pure tone stimuli; (2) stimulus frequency and attenuation settings; (3) display of subject instructions and response touch-buttons; (4) recording of subject responses for program control; (5) logging of subject responses into data files; and (6) main computer screen display for monitoring test status, progress, and results.

Database driven architecture. The main computer control program was designed from the ground up to be entirely driven by a Microsoft Access desktop database. Information stored in database tables controls the main program operation including parameters for testing protocols, timing intervals,

frequency sets, level-based step sizes, randomization ranges, numbers of steps, numbers of averages, instrumentation used, etc. The testing system is therefore easily configurable by non-programmers for modification of experimental protocols. Detailed testing data are logged directly into tables during program operation. Data logged include stimulus presentation history, responses, and intermediate and final averaged results. Results and associated testing parameters are easily queried off-line for subsequent analysis.

Results

Computerized testing algorithms. Various testing algorithms are selectable with this system for automated tinnitus matching. Two companion papers are presented in these Proceedings. The first ("Tinnitus loudness and pitch matching: various techniques with a computer-automated system") reports comparative results of pitch matches obtained using three different automated protocols, and a manual protocol controlled with the same system. The second paper ("Masking curves and otoacoustic emissions in subjects with and without tinnitus") describes how the system was adapted to obtain masking audiograms which are similar to psychoacoustical tuning curves.

Discussion and conclusion

The field of clinical audiology has uniform testing protocols for quantification and diagnosis of hearing loss. Test results from one clinic can be readily interpreted by audiologists in any other clinic. For the patient with tinnitus, however, there is no standard protocol for tinnitus evaluation. It is therefore imperative to establish uniform methodology for a clinical battery of tests to quantify patients' tinnitus sensations. We believe such standardization would improve both research and clinical treatment for tinnitus, ultimately benefitting the tinnitus patient.

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Comparison between matched and self-reported change in tinnitus loudness before and after tinnitus treatment

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Tinnitus loudness in 100 ears of 73 patients with subjective tinnitus were measured before and after treatment and compared to self-reported changes in tinnitus loudness. Loudness matching test was performed at increments of one to two decibels in both the contralateral ear and the ear with tinnitus using an audiometer. Self-reports of the change in tinnitus loudness were expressed by the 10-scale method. As a result, moderate correlations were found between self-reported changes in tinnitus loudness and loudness match values. However, when frequencies of tinnitus differed before and after treatment, these correlations were low. In the group of patients with the same tinnitus frequencies after treatment as those before treatment, moderate correlations were again obtained between self-reported change in tinnitus loudness and the loudness match values. Therefore, focusing attention not only on tinnitus loudness but also on changes in tinnitus frequency is necessary to properly evaluate changes in tinnitus loudness after tinnitus treatment.

Introduction

Tinnitus is expressed by loudness and frequency matched by audiometer or tinnitus synthesizer. As tinnitus is a subjective complaint, it is considered very important to evaluate the relationship between self-reported loudness and the result obtained by loudness match test. Furthermore, it is also important to estimate the effect of tinnitus treatment not only by subjective assessment but also matched loudness of tinnitus. This study compared the relationship between matched and self-reported changes in tinnitus loudness before and after tinnitus treatment.

Methods

Tinnitus loudness in 100 ears of 73 patients with subjective idiopathic tinnitus who visited Fukui Medical University Hospital were matched before and after tinnitus treatment and compared to self-reported changes in tinnitus loudness. The mean

age was 53 years, with a range of 28 to 75 years including 37 men and 36 women. Underlying diseases were unknown sensorineural hearing loss (31 cases), presbycusis (18 case), noise-induced hearing loss (8 cases), sudden deafness (6 cases), Meniere's disease (5 cases), chronic otitis media (3 cases), post-traumatic sensorineural hearing loss (2 cases) and acoustic trauma (1 case). Tinnitus was controlled by combined treatment with drugs such as tranquilizers, anticonvulsants, anesthetics, muscle relaxant and calcium channel-blocking agents.

Loudness match testing was performed in increments of 1 to 2 decibels in both the contralateral ear and the ear with tinnitus using a clinical audiometer (AA63-N, RION, Japan). Loudness was matched in both the contralateral ear and the ear with tinnitus, if tinnitus was unilateral. Percentage for change in matched loudness was calculated as (loudness after treatment/loudness before treatment) = 100. Self-reports of the change in tinnitus loudness were expressed by the 10-scale method. Percentage for change in self-reported loudness was calculated as (self-reported loudness after treatment/self-reported loudness before treatment) × 100. All matched loudness of tinnitus was measured before and 4 weeks after treatment.

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Results

Tinnitus loudness before and after treatment

Matched loudness of tinnitus before and after treatment is shown in Figure 1. In 70% of patients, tinnitus loudness decreased after treatment.

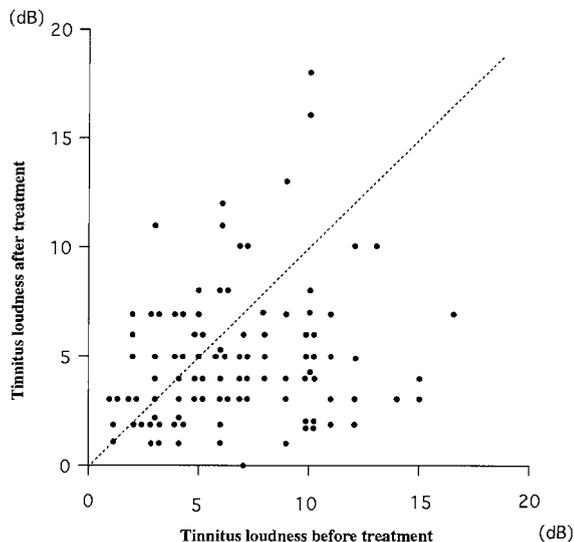


Figure 1 Distribution of tinnitus loudness before and after treatment (n = 100).

Correlation between matched and self-reported changes in tinnitus loudness

When tinnitus loudness was matched in the ear with tinnitus, moderate correlations were found between self-reported changes in tinnitus loudness and loudness match values (Figure 2). Furthermore, moderate correlations were also found between self-reported changes in tinnitus loudness and loudness match values, when tinnitus loudness was matched in the ear contralateral to that with tinnitus (Figure 3). Table 1 shows the results of correlation between self-reported changes in tinnitus loudness and loudness match values. Moderate correlation were found not only in changes in matched values of tinnitus loudness in the contralateral ear or the ear with tinnitus but also in better or worse hearing ears compared with self-reported changes.

Influence of tinnitus frequency change on matched tinnitus loudness

Figure 4 was converted from Figure 2 according to

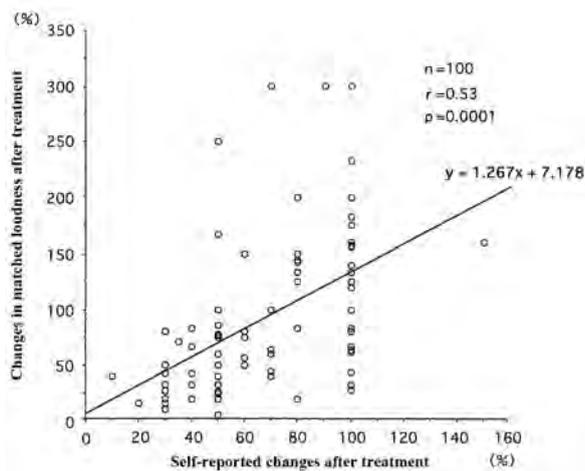


Figure 2 Correlation between self-reported changes in tinnitus loudness and changes in matched loudness after treatment (Ipsilateral ear with tinnitus).

differences of tinnitus frequency before and after treatment. Cases with changes of tinnitus frequency were divided into two groups according to whether frequency changes were within or over one octave. In comparison to the group without change in tinnitus frequency, when frequencies of tinnitus dif-

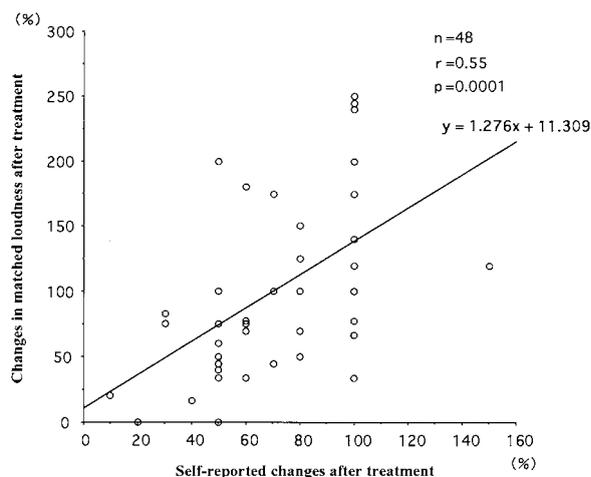


Figure 3 Correlation between self-reported changes in tinnitus loudness and changes in matched loudness after treatment (Ear contralateral to that with tinnitus).

fered before and after treatment, correlation between self-reported loudness change and loudness match values was low. In the group of patients with the same tinnitus frequencies after treatment

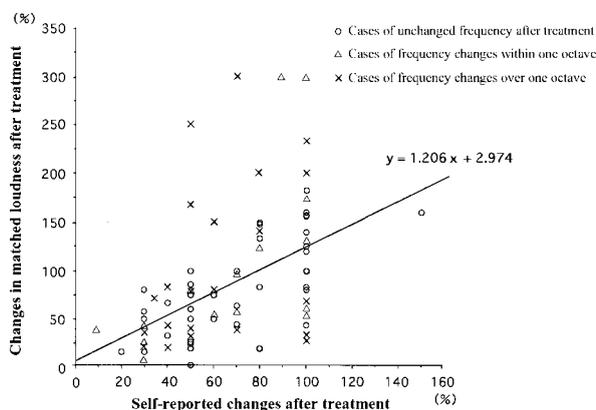
Table 1 Correlation between self-reported changes in tinnitus loudness and changes in matched loudness after treatment

| | Number of cases (n) | Correlation coefficient (r) | Level of significance (p) | Regression parameters | Regression intercepts |
|---|---------------------|-----------------------------|---------------------------|-----------------------|-----------------------|
| Ear with tinnitus | 100 | 0.53 | 0.0001 | 1.27 | 7.18 |
| Ear contralateral to that with tinnitus | 48 | 0.55 | 0.0001 | 1.28 | 11.31 |
| Better hearing ear | 48 | 0.56 | 0.0001 | 1.16 | 19.65 |
| Worse hearing ear | 48 | 0.58 | 0.0001 | 1.27 | 1.51 |

Table 2 Correlation between self-reported changes in tinnitus loudness and changes in matched loudness after treatment (Cases of unchanged frequency after treatment).

| | Number of cases (n) | Correlation coefficient (r) | Level of significance (p) | Regression parameters | Regression intercepts |
|---|---------------------|-----------------------------|---------------------------|-----------------------|-----------------------|
| Ear with tinnitus | 48 | 0.64 | 0.0001 | 1.21 | 2.97 |
| Ear contralateral to that with tinnitus | 25 | 0.67 | 0.0001 | 1.39 | 5.82 |
| Better hearing ear | 25 | 0.69 | 0.0001 | 1.29 | 2.75 |
| Worse hearing ear | 25 | 0.6 | 0.002 | 1.02 | 12.06 |

as that before treatment, however, moderate correlations were again obtained (Table 2). All coefficient values in Table 2 were found to be improved compared with those in Table 1. The highest correlation ($r = 0.69$) was obtained on the side of the better hearing ear.

**Figure 4** Correlation between self-reported changes in tinnitus loudness and changes in matched loudness after treatment (Ear with tinnitus, Classification by frequency change). Regression line was calculated from data of cases with unchanged frequency (O).

Discussion

It has been reported that correlations between self-reported loudness and loudness match values were usually small, even when significant [1]. Against this, there are some reports showing improved correlation of matched and self-reported loudness of tinnitus [1,2]. To date, there was no report to evaluate the relationship between self-reported changes in tinnitus and changes in matched loudness before and after treatment. Although correlation between matched and self-reported tinnitus loudness after treatment was moderate in this study, it was clarified that change in tinnitus frequency after treatment made the correlation worse. As one of the reasons why correlation between loudness before tinnitus treatment and that after treatment decreased when frequencies of tinnitus changed after treatment, the theory that loudness depends on frequency is cited [3]. If the frequency of tinnitus changed after treatment, loudness would also change and it might become difficult to compare tinnitus loudness before and after treatment.

Another reason is the phenomenon of loudness recruitment [4,5]. Since tinnitus loudness is expressed as the sensation level, it is affected by recruitment. For instance, small loudness measured at the tinnitus frequency with recruitment before treatment might change to a large value if loudness after treatment is measured at frequency without recruitment. In this study, tinnitus loudness was measured in the better and worse hearing ears to evaluate the effect of loudness recruitment. However, there was no difference between better and worse hearing ears. It was considered that this was because of the existence of recruitment phenomenon even in better (but not normal) hearing ears. Further study is needed to find what other factors besides frequency changes and loudness recruitment might contribute to the discrepancy between loudness matches and subjective judgement of tinnitus loudness [5].

In conclusion, it was considered that attention not only to tinnitus loudness but also to changes in tinnitus frequency is necessary to properly evaluate change in tinnitus loudness after tinnitus treatment. That is to say that matched tinnitus loudness is reliable, when tinnitus frequency after treatment is the same as that before treatment. However, there is a possibility that matched loudness differs from self-reported loudness, when tinnitus frequency changes after treatment.

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Tinnitus in normal hearing adults: A study on the central auditory processing function and the handicap

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The objective of this study was to investigate central auditory function in peripheral normal hearing adults with tinnitus complaint. We investigated 20 subjects with tinnitus complaint and peripheral hearing within normal limits, attended in an audiological clinic in São Paulo, Brazil. All the subjects were submitted to: Speech in Noise Test; Filtered Speech Test; Binaural Fusion Test; Staggered Spondaic Words Test – SSW; Masking Level Difference – MLD. Tinnitus patients were also submitted to the Tinnitus Handicap Inventory. In relation to the low redundancy monaural tests, tinnitus patients performed significantly poorer than subjects without tinnitus. The Binaural Fusion test showed no differences between the groups, even though we observed a higher occurrence of MLD abnormalities in the tinnitus group. In the SSW test, the groups were qualitatively different.

Introduction

In the past, people believed that tinnitus was exclusively a Peripheral Auditory System phenomenon. Today, studies show us that tinnitus, as any peripheral disturbance, may also modify Central Auditory Nervous System functions.

An interesting and curious fact is that tinnitus seems not to be only associated to the auditory cortex, but to other cortical areas related to emotion and, even with hallucination.

In audiological clinics, many patients report difficulty in hearing and interference of tinnitus with their ability to understand speech. They believe that with the end of tinnitus their communication problems would vanish.

When these patients are submitted to conventional audiological tests (pure tone audiometry, speech audiometry and acoustic immittance), results may be within normal limits for peripheral hearing, even though they have this hearing difficulty complaint.

Central auditory processing tests, unlike conventional tests, are sensitive to central auditory system dysfunction, since they modify the acoustic signal, reducing its redundancy.

If tinnitus is an auditory dysfunction it may reduce the central auditory system's multiplicity of

pathways (intrinsic redundancy) which may result in difficulty to understand speech.

The objective of this study was to investigate central auditory function in peripheral normal hearing adults with tinnitus complaint.

Method

In this study, we investigated 20 subjects with tinnitus complaint and peripheral hearing within normal limits attended in an audiological clinic in São Paulo, Brazil and compared them to a control group.

The experimental group consisted of 04 male and 16 female subjects, with ages ranging from 20 to 53 years old (mean 36.1, SD \pm 9.1). All subjects presented:

- hearing thresholds better than or equal to 20 dB HL from 0.25 to 8 KHz;
- speech recognition score better than or equal to 92%;
- type A tympanogram;
- acoustic reflex present.

Both groups presented normal otoscopy with no otologic problems, metabolic disease, and dizziness or noise exposure.

All the subjects (control and experimental groups) were submitted to a central auditory function assessment, which included:

- Speech in Noise Test;

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- Filtered Speech Test;
- Binaural Fusion Test;
- Staggered Spondaic Words Test – SSW;
- Masking Level Difference – MLD.

Tinnitus patients were also submitted to:

- Tinnitus Handicap Inventory (Newman, Jacobson and Spitzer, 1996);
- Pitch and loudness psychoacoustic characterization of tinnitus (Vernon & Scheullening, 1978).

The equipment used was:

- Oscope;
- Two channel audiometer Interacoustics AC40;
- Middle ear function analyser Interacoustics AZ 26;
- The speech tests were recorded in a compact disc and they were translated and adapted to Portuguese by Machado (1996).

Results

In relation to the low redundancy monaural tests (Speech in Noise and Filtered Speech), tinnitus patients performed significantly poorer than subjects did without tinnitus did. In the Speech in Noise Test, the mean score of tinnitus patients was 94.5% in the right ear and, 98.25% in the left ear and, in the control group it was 100% in both ears ($p = 0.0001^*$ right ear/ $p = 0.0088^*$ left ear). In the Filtered Speech Test, the mean score of tinnitus patients was 98.5% in both ears (S.D. = ± 3.29), in the control group it was 100% in both ears (S.D. = ± 0.00) ($p = 0.0376^*$).

The Binaural Fusion test showed no differences between the groups. the mean score of tinnitus patients was 94.5% in the right ear and, 98.25% in the left ear and, in the control group it was 100% in both ears. In the Filtered Speech Test, The mean score of tinnitus patients was 99.25% in the right ear (SD = ± 2.45) and 99.5% in the left ear (SD = ± 1.54) and, in the control group it was 100% in both ears (SD = ± 0.00) ($p = 0.00, 1521$).

MLD was similar in both groups at 0.5 kHz and at 1.0 kHz. Tinnitus patients presented a mean MLD of 14.75 dB (SD = ± 6.38) and the control group presented a mean MLD of 14.75 dB (SD = ± 2.55) at 0.5 kHz. At 1 kHz, tinnitus patients presented a mean MLD of 9.45 dB (SD = ± 5.16) and the control group presented a mean MLD of 11.50 dB (SD = $\pm 2,86$).

In the SSW test, the groups were qualitatively different, mainly because tinnitus subjects showed a higher number of reversals. 50% of the tinnitus patients and 25% of the control group presented high number of reversals ($\chi^2 = 2.67, p = 0.1025$).

In relation to the SSW quantitative analysis, 2 tinnitus subjects presented mild to moderate abnormalities ($p = 02308$).

We found a higher occurrence of bilateral tinnitus (60% of tinnitus patients) and, an average pitch of 3.76 kHz in the right ear (SD = ± 2.66) and 3.8 kHz in the left ear (SD = ± 2.12). Average loudness was

31.18 dB HL (SD = ± 11.39) in the right ear and 26.18 dB HL (SD = ± 9.93) in the left ear. These results are in agreement with literature.

The average handicap score in the tinnitus subjects was 28.5 (SD = ± 19.69), ranging from 8 to 62, showing a mild handicap.

Handicap scores were higher in patients with a recent tinnitus complaint ($p = 0.7645$) and in subjects with higher number of reversions in the SSW test. 40% (SD = ± 19.34) of tinnitus patients with higher handicap presented high number of reversals ($p = 0.005^*$). Loudness also showed a significant correlation with handicap ($p = 0.0062^*$).

Conclusions

The Central Auditory Processing results obtained in the tinnitus subjects are in agreement with literature (Newman *et al.*, 1994; Goldstein & Shulman, 1995).

It is possible to observe that tinnitus may interfere in speech perception, maybe acting as a masking noise. Maybe tinnitus patients' auditory efferent pathways are most likely to fail in the task of detecting speech in background noise.

The Central Auditory Processing assessment results suggest Brainstem dysfunction and may contribute to the idea of tinnitus as a peripheral disturbance that interferes in central auditory function.

Literature data on handicap caused by tinnitus are not similar to our findings, but it is important to emphasize that our subjects presented peripheral normal hearing, and the majority of tinnitus studies are on hard-of-hearing patients.

Tinnitus seems not to cause a great handicap when it is not associated with hearing loss, even though it is annoying and stressing.

We conclude that:

- 1 In the low redundancy monaural tests (Filtered Speech and Speech in Noise Tests), tinnitus patients performed significantly worse than control group;
- 2 The Binaural Fusion Test showed no differences between the two groups;
- 3 In the SSW Test, the groups were qualitatively different, mainly because the experimental group showed a higher number of reversals;
- 4 In the quantitative analysis, 2 tinnitus patients presented mild to moderate abnormalities;
- 5 We observed a higher occurrence of MLD abnormalities in the tinnitus group;
- 6 We found a higher occurrence of bilateral tinnitus than monaural;
- 7 Average pitch of 3.76 kHz in the right ear and 3.8 kHz in the left ear;
- 8 Average loudness was 31.18 dB HL in the right ear and 26.18 dB SL in the left ear;
- 9 The average handicap score in tinnitus subjects was 21, ranging from 8 to 62, showing a mild handicap;
- 10 Handicap scores were higher in subjects with recent tinnitus complaint;

11 Handicap scores were higher in subjects with higher number of reversions in the SSW test. Loudness also showed a significant correlation with handicap.

We emphasize the necessity of including the Central Auditory Processing Tests in the assessment of tinnitus patients, since it may give support to the hearing difficulty complaint of the tinnitus subjects and be of great value in the assessment of the central auditory function in these patients.

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Effects on DPOAE of extended exposure to salicylate: A peripheral correlate of salicylate-induced tinnitus ?

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The objectives of this study was to reveal the effects of extended exposure to salicylate on active mechanisms of the outer hair cells (OHC). Amplitudes of distortion product oto-acoustic emission (DPOAE) were recorded at several f_2/f_1 ratio, with f_2 equal to 11 kHz. Contrary to many studies which reported a decrease in DPOAE amplitude as an acute effect of salicylate, an increase in amplitude of $2f_1-f_2$ DPOAE was observed when chronic effect is scrutinated. The OHC hyperactivity could be at the origin of an aberrant neuronal signal interpreted by the centers as tinnitus. We suggest that the long-term effect of salicylate and not the acute one, would be predominant in salicylate-induced tinnitus.

Introduction

Several hypotheses have been put forward to account for the pathophysiological mechanisms of tinnitus, but none have been proven yet [1]. There is a consensus that tinnitus is the consequence of aberrant neural activity within the auditory pathways and that such activity is interpreted as sound in auditory centers [1]. Nevertheless, there is a variety of mechanisms leading to an aberrant neuronal activity which could induce tinnitus. It is assumed that, in the majority of cases, the aberrant neuronal signal associated with tinnitus is generated at the cochlear level, by organ of Corti dysfunction (hearing loss, ototoxic drug . . .). Ototoxic drugs, as salicylate, creating irreversible or reversible damages at the cochlear level can induce tinnitus in man [2,3] or animals [4].

The literature supports the hypothesis that salicylate predominantly impacts the OHC by deactivating active processes [5]. Acute administration of salicylate reduces amplitude of the transient and spontaneous oto-acoustic emissions (OAE) [6,7]. This action on the OHC system could be frequency dependent [8].

Whereas acute effects of salicylate have been largely studied, long-term effects have received little interest. It is very important to note that, in humans,

high doses of salicylate can induce tinnitus, with the maximum effect after several days of treatment [9,10]. Cazals *et al.* [11] studied acute and chronic effects of salicylate on spontaneous auditory nerve activity. They observed an acute decrease in the average spectrum of electrocochleoneural activity (ASECA) during several hours after salicylate injection, and in contrast, an increase of neuronal activity over days of treatment in the long-term condition. Thus, the salicylate effect on the auditory nerve appears to be opposite, according to acute or long-term exposure to the drug are involved.

The aim of our study was to look for a peripheral correlate of increase in ASECA observed by Cazals *et al.* [11] after extended exposure to salicylate using distortion product otoemission (DPOAE). We studied the $2f_1-f_2$ DPOAE with f_2 equal to 11 kHz, the presumed pitch of salicylate-induced tinnitus, as measured by Jastreboff and Brennan [4].

Methods

Experiments were performed on pigmented rat (Dark agouti) of male sex weighing between 200 and 250 g. Animals from "salicylate group" ($n = 8$) received daily injection of salicylate (s.c.) at a concentration of 350 mg/Kg dissolved in saline in a total volume of 500 μ l during 7 days. Animals from "control group" ($n = 7$) received saline injection (s.c.) in a total volume of 500 μ l during the same time as the salicylate group. Animals were anesthetized with chloral hydrate (300 mg/kg i.p.).

In the two groups, DPOAE responses were

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recorded, before treatment, 24 and 72 hours after the last injection of salicylate. All recordings were made in a sound treated room. DPOAEs were recorded using an Otodynamics ILO92 Analyser and a neonate ILO92 DPOAE probe with three ports. The probe was sealed in the external auditory meatus. DPOAEs with f_2 fit at 11 kHz and f_2/f_1 equal successively to 1.31, 1.34, 1.37, 1.40 and 1.44 were studied. For each f_2/f_1 ratio, we recorded input/output function using 5 different intensities. The levels of f_1 (L1) was 54 dB SPL, 51 dB SPL, 48 dB SPL, 45 dB SPL and 42 dB SPL with respectively L2 (level of f_2) equal to L1 minus 5 dB SPL.

We tested the difference between the two groups in term of DPOAE amplitude using ANOVA with repeated measures (recording session and intensity as repeated factors with group as the independent factor) for each f_2/f_1 ratio. Post-hoc test (Fisher's test) was used to test the group effect for each combination of factors. For each f_2/f_1 ratio, for each group, and for each day of recording, linear regression was calculated using the least square fit method. The slope of the linear regression was computed on statistical analysis only when $p < 0.05$. ANOVA repeated measures (recording session and

f_2/f_1 as repeated factors with group as independent factor) was used to compare differences between the two groups in term of slope of input/output function. Fisher's test was performed to reveal the group effect as a function of f_2/f_1 ratio.

Results

The two groups were different for f_2/f_1 ratio equal to 1.31 ($p = 0.001$) and 1.34 ($p = 0.003$). One day after the last injection of salicylate, DPOAE amplitude was significantly increased in salicylate group compared to control group, at each stimulus intensity. Averaged DPOAE amplitudes obtained in salicylate group and control group, in function to stimulus intensity, are shown in Figure 1 ($f_2/f_1 = 1.31$).

We compared also the slope of input/output function obtained from the two groups. For the $f_2/f_1 = 1.31$ and $f_2/f_1 = 1.34$ the slope was significantly decreased in salicylate group. However, three days after the last injection of salicylate, neither DPOAE amplitude nor slope of input/output function showed any significant group effect.

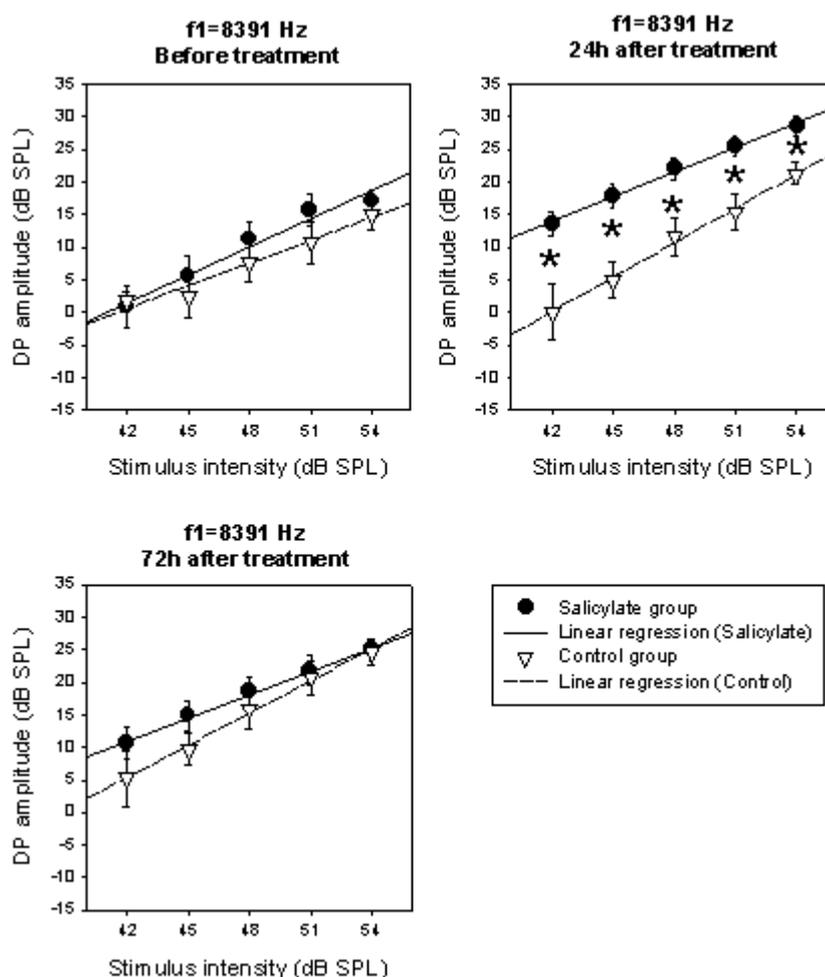


Figure 1 Mean $2f_1-f_2$ amplitude (SEM) when $f_2/f_1 = 1.31$ at the various stimulus intensities in control group ($n = 7$) and salicylate group ($n = 8$) (*: $p < 0.05$).

Discussion and conclusion

Extended exposure to salicylate induced changes in DPOAE amplitude. Our results confirm the view derived from previous human and animal experiments that salicylate acts on the outer hair cells. The slope of input/output function decreased because the increase of 2f₁-f₂ amplitude was stronger at low levels of the primaries. This result is also consistent with a salicylate effect on OHC motility, because the contribution of active mechanisms is stronger at low levels of stimulation. However, contrary to many studies which reported a decrease in DPOAE or OAE amplitude as an acute effect of salicylate [6,7,8], an increase in amplitude of 2f₁-f₂ DPOAE is observed when the chronic effect is considered.

These changes in OHC properties could be the peripheral correlate of the enhanced average spectrum electrophysiological cochleoneural activity (ASECA) observed by Cazals *et al.* [11]. In the acute condition, the authors observed a decrease in the ASECA-1-kHz peak during several hours after the administration of salicylate. In contrast, in the long-term condition (records achieved 1 day after the last injection of salicylate), there is an increase over days of treatment. Cazals *et al.* [11] postulated that electrophysiological modifications reflect the presence of salicylate-induced tinnitus.

We suggest that the increase of DPOAE amplitude observed after an extended exposure to salicylate, may be a physiological correlate of the presence of tinnitus at cochlear level. Finally, what could be important in salicylate treatment and in its ability to induce tinnitus, is that this occurs specifically after an extended exposure rather than acute exposure to the drug. In humans, during long-term salicylate treatment, tinnitus occurs preferentially after several days, and becomes louder as treatment is continued [2,3,9]. Penner [7] proposed that acute effects of salicylate could abolish spontaneous otoacoustic emissions and subsequent tinnitus. These studies strengthen our postulate that what is critical in salicylate-induced tinnitus is the nature of the exposure to the drug, and particularly its duration.

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Serum zinc level in patients with tinnitus

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We examined the serum zinc level in patients suffering from tinnitus. Blood zinc levels were measured in 181 patients with tinnitus. Seventy-eight patients who had received administration of any drugs or had been affected by other diseases were excluded. Because patients aged between 20 and 59 years old were selected, the residual 73 patients were mainly analyzed.

Thirty-eight healthy volunteers were allotted for the control group. There was a significant decrease ($p < 0.01$) in serum zinc levels in patients with tinnitus having no hearing loss compared with the control group. Statistical tests revealed a significant correlation between the average hearing levels and serum zinc levels.

Introduction

Zinc is one of the essential trace elements known to play an important role in human living cells and it was first recognized as an essential electrolyte minerals for rats in 1934 by Todd and for human in 1961 by Prasad *et al.* [1]. Shambaugh Jr. found that soft tissues of guinea pigs' inner ear have the highest zinc content of any organ or tissue in body and the zinc deficiency may also results in some functional inner ear disorders [2]. He also suggested that organs and tissues showing highest content of a particular essential trace element will be likely to show the greatest functional and structural changes due to its deficiency. The zinc deficiency may also cause some functional inner ear disorders such as sensorineural hearing loss, imbalance, and tinnitus. He reported that 25% of patients underwent the diminution of tinnitus and at least 20% of patients showed a significant improvement in pure-tone hearing by the supplement with zinc. In addition, he suggested that zinc deficiency increases after the age of 60 years old, and may be an etiologic factor in some cases of presbycusis, tinnitus, and imbalance [3]. Gersdorff *et al.* examined 115 patients suffering from tinnitus and 79 patients (68.7%) were found to have hypozincemia [4]. They found no particular correlation between the nature of tinnitus and hypozincemia except for continuation of the head noises. While Paaske *et al.* reported that there was no significant difference in the improvement of

tinnitus between the zinc group and the placebo group [5].

The purpose of this study was to measure serum zinc levels in patients suffering from tinnitus.

Subjects and methods

Initially 181 patients suffering from tinnitus participated in this study. However, 78 patients who had received an administration of various kinds of drugs or had been affected by other diseases were excluded as unsuitable subjects for the following studies. In addition, patients' ages were restricted between 20 and 59 years old because of the potential effect of aging. Consequently, 73 patients consisted of 50 females (68.5%) and 23 males (31.5%) were mainly investigated as subjects. The mean age was 42.7 years (standard deviation, 11.0 years). All patients were examined at the outpatient clinic of otolaryngology St Marianna University Toyoko Hospital. A blood sample was taken to determine serum zinc levels. Thirty-eight healthy volunteers consisted of 26 females and 12 males were allotted as the control group. The mean age of control group was 42.4 years old and standard deviation was 9.7 years old.

Statistical tests were based on Mann-Whitney U test and linear regression analysis. Differences or changes at the $p < 0.05$ level were considered significant. All tests were performed using the StatView 5.0 J package for power Macintosh.

Results

The serum zinc level of patients with tinnitus was 88.1 ± 12.4 $\mu\text{g/dl}$ and that of the control was 92.5 ± 10.6 $\mu\text{g/dl}$. This difference was close to the statistic-

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ally significant level ($p = 0.06$). Based on the extent of serum zinc levels for the control group, the level under $79.7 \mu\text{g/dl}$ (mean -1 S.D.) was determined as hypozincemia. Twenty-one of 73 patients (28.8%) was determined as hypozincemia.

We divide patients into two groups, tinnitus with normal hearing and tinnitus with hearing loss. Normal hearing was defined that the hearing thresholds between 250 Hz and 4 kHz were all within 20 dB. The serum zinc level of patients with normal hearing and that with hearing loss were $83.1 \pm 10.7 \mu\text{g/dl}$ ($n = 24$) and $90.6 \pm 12.5 \mu\text{g/dl}$ ($n = 49$), respectively. The mean ages for patients with normal hearing and patients with hearing loss were 41.3 ± 10.3 and 43.4 ± 11.4 years. The difference in serum zinc level between patients with normal hearing and control was statistically significant ($p < 0.01$). There is also significant difference in serum zinc level between patients with normal hearing and patients with hearing loss ($p < 0.05$). However, the difference in serum zinc level between patients with hearing loss and control was not significant ($p = 0.42$). Figure 1 illustrates the relation between patient's serum zinc level and average hearing acuity at five frequencies from 250 Hz to 4 kHz. A regression analysis showed a significant relation between two values ($r^2 = 0.15$, $p < 0.001$).

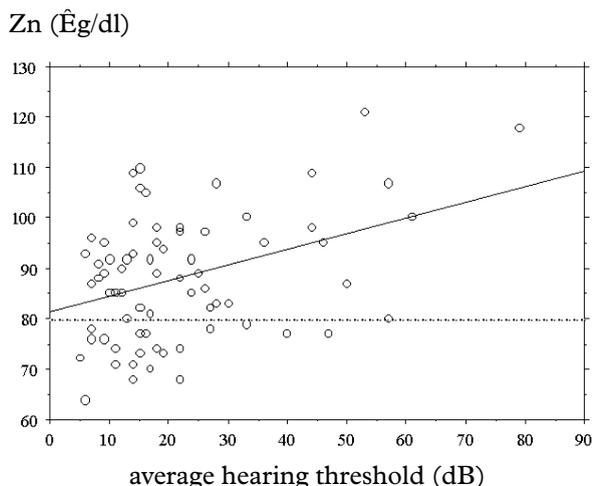


Figure 1 Scattergrams showing the correlation between average hearing thresholds on pure tone audiograms and serum zinc levels. Horizontal line indicates lower limit of normal serum zinc level.

Discussion

The generating mechanism of tinnitus remains obscure [6]. Abnormal neural synchronization was suggested to be responsible for induction of tinnitus [7,8]. Ochi and Eggermont [9] examined the spontaneous firing in cat's primary auditory cortex before and after application of salicylate and found the abnormal synchronization between cells after the drug administration. In addition, the same tendency was demonstrated after the administration of quinine [10]. Changes in Ca^{2+} conductances of cortical or thalamic pyramidal cells were supposed

to result in abnormal synchronization. Taking the same group of cation into account, zinc may play some role in regulation of Ca^{2+} conductances. Zinc deficiency may cause changes in calcium channel conductance.

The number of hypozincemia in tinnitus patients in our result (28.8%) was lower than that of a previous report (67.8%: Gersdorff *et al.*). The difference of subjects selection and extent of normal range might be responsible. Gersdorff *et al.* examined a group of 115 tinnitus patients and 79 patients (68.7%) were found to have hypozincemia [4]. Shambaugh Jr. suggested the usefulness of zinc supplement in tinnitus patients [2]. While Paaske *et al.* reported using double-blind, randomized, placebo-controlled trial that there was no significant difference in the improvement of tinnitus between zinc group and placebo group [5]. The degree of patient's zinc level seemed to exert an influence on these different results. Shambaugh Jr. [2,3] and Gersdorff *et al.* [4] observed hypozincemia in many patients while Paaske *et al.* [5] found it in only one patient. These results suggests that zinc supplement would be useless for patients without hypozincemia.

Zinc was reported to prevent the salicylate-induced hearing impairment [11]. We found significant decrease in serum zinc level in many patients with tinnitus despite normal hearing. On the contrary we observed the normal level in many patients with tinnitus and hearing loss. Consequently, the zinc deficiency is supposed not to relate to hearing loss but to tinnitus. Zinc deficiency might relate to the disorder in non-lemniscal pathway as suggested by Møller [12].

Our results suggest that zinc deficiency may induce the generation of tinnitus in some cases, especially whose hearing thresholds are within normal. It is necessary to measure serum zinc level to classify patients into several groups based on their pathology such as zinc deficiency, vascular disorder, endolymphatic hydrops, acoustic tumor and others, because we should select the appropriate therapy for tinnitus in these groups.

Conclusion

The serum zinc level in patients with tinnitus despite normal hearing was significantly lower than that in the control group. About 30% of patients revealed hypozincemia which was defined as lower level than normal control limits. Statistical tests revealed a significant correlation between the average hearing threshold on pure tone audiogram and the serum zinc level.

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The management of persistent tinnitus after the treatment of sudden deafness: The effect of intravenous lidocaine and oral carbamazepine

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Objectives: The hearing loss due to sudden deafness is frequently associated to the presence of constant tinnitus. The treatment aims the restoration of the auditory thresholds, and tinnitus is usually a secondary concern. Even when the hearing doesn't recover to normal levels, the persistence of tinnitus may become the main patient's complaint. The objective of the study was to evaluate the effect of the intravenous lidocaine in patients with persistent tinnitus after the routine treatment of sudden deafness, and the effectiveness of its substitution for carbamazepine as a long-term treatment.

Methods: The authors studied 24 patients with past history of treated sudden deafness who persisted with constant tinnitus, independent of their audiometric results. There were 15 females and 9 males, whose ages varied from 29 to 66 years (average 44, 95 years). Tinnitus severity was evaluated according to the visual-analogue scale into mild, moderate and severe. The injection of 2% intravenous lidocaine was accomplished in a silent chamber for better perception of the variations of the tinnitus, using 1 mg/Kg in 3 minutes. The results were classified into abolition, improvement, unaffected or worsen. The patients with favorable results (abolition + improvement) were advised to use oral carbamazepine for 2 months in ascending doses (from 100 to 600 mg/day), and the results regarding tinnitus were classified by the same criteria as used for lidocaine.

Results: Tinnitus was classified as mild in 2 cases, moderate in 8 and severe in 14 cases.

The lidocaine: Out of 24 patients, 6 had abolition of tinnitus after the intravenous lidocaine, 14 had improvement, 2 were unaffected and 2 worsened, totaling 20 cases with favorable results (abolition + improvement). Among the 14 cases with severe tinnitus, 12 presented favorable results, as well as 7 out of the 8 cases with moderate tinnitus. Thus, the lidocaine presented favorable results in general in 83.3% of the cases of sudden deafness, 85.7% of severe tinnitus and 88.8% of moderate tinnitus.

The carbamazepine: Out of the 6 cases with temporary abolition after the lidocaine, 5 used carbamazepine, and 4 showed improvement with this long-term treatment (80%). Out of the 14 cases with temporary improvement after lidocaine, 12 used carbamazepine, and 7 maintained this improvement in tinnitus (58.3%).

Conclusions: The intravenous lidocaine is an effective method for relief of the persistent tinnitus after sudden deafness in 83.3% of the cases, improving the annoyance referred by the patient, even if temporarily. The oral carbamazepine as a long-term treatment in those patients allowed an improvement in 64.7%, although none has presented abolition of tinnitus. Our results are exciting and make us concern about the possible advantages of the use of the intravenous lidocaine test associated to the classic treatment of the sudden deafness, in an attempt of also prioritizing the presence of tinnitus, and not just the hearing loss.

Introduction

Defined as a sudden idiopathic loss of at least 30 dB in three consecutive frequencies in up to three days,

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the sudden deafness is still considered an enigma to the otorhinolaryngologists [1,2,3]. Infectious, vascular and autoimmune processes have already been proposed as possible mechanisms to explain it [2,3].

The prognostic regarding the recovery of pure-tone thresholds is quite well established. Most of the clinical studies previously performed and most of the treatments already suggested primarily aimed

the restoration of the tonal thresholds and the discrimination of the affected ear [1,3,4]. Tinnitus is usually a secondary concern.

When there is no counterindication, patients with sudden deafness for less than 10 days are usually interned in our service to receive intravenous Dextran associated to vasodilator, vitamin A, corticosteroid and antivirus drugs, according to the case. At the same time, all cases are submitted to laboratory and radiological investigation.

The evolution with concomitant or later appearance of tinnitus has been quite homogeneous in our experience, regardless of the etiology of the sudden deafness. After the treatment of this "acute phase", independently of the recovery of hearing thresholds, sometimes the main complaint is not the hearing loss anymore (even when still present), but the tinnitus, which may interfere with the patient's quality of life and lead to psychological disorders. Thus, the treatment of this persistent tinnitus secondary to sudden deafness is a difficult task.

Tinnitus is generally attributable to an abnormal neuronal activity within the auditory pathways. Considering the membrane stabilizing effect of local anesthetics, lidocaine may modulate these abnormal activity, promoting tinnitus relief. Indeed, several studies have already proved the effect of intravenous lidocaine on tinnitus [5-12]. Though, because of its transient effect, the substitution for an oral medication is desired in order to maintain its effect. This is the case of the anti-convulsants. Although their mechanism of action is different from that of lidocaine, they also inhibit the hyperactivity of the auditory pathways [13].

Thus, the positivity to the test is considered as a favorable prognostic to the use of oral anticonvulsants, such as carbamazepine [14,15]. In our previous study, the test has been effective in 76% of patients with tinnitus due to many different etiologies [6]. Among these patients with a positive test, 50% showed favorable results with oral carbamazepine in alleviating tinnitus. Believing that the test might bring a new approach to patients with sudden deafness, we decided to evaluate the cases with this specific diagnosis, once the early tinnitus treatment could increase the rate of success.

The purpose of this study was to evaluate the effect of the intravenous lidocaine in patients with persistent tinnitus after the treatment of sudden deafness, and the effectiveness of its substitution for oral carbamazepine in the long-term treatment.

Methods

Twenty four patients with tinnitus due to sudden deafness were enrolled in this study from January 1997 to December 1998. There were 15 women and 9 men whose age varied from 29 to 66 years (average of 49.9 years).

All patients have previously been submitted to the treatment of sudden deafness within the first 10 days of symptoms with no improvement of the tinnitus, independently of the improvement of the

pure-tone thresholds. The previous treatment of the sudden deafness was performed in the Clinics Hospital of University of São Paulo, as well as this study.

All patients answered to a tinnitus questionnaire, and its severity was classified according to the visual scale in mild, moderate and severe. The patients were submitted to the lidocaine test, that is, the administration of 2% intravenous lidocaine in the dose of 1 mg/Kg for 3 minutes, in a silent chamber for better perception of the changes in tinnitus loudness. After the test, the results were classified into abolition, improvement, unchanged or worsen of the tinnitus. Then, the patients with positive results to the test (abolition or improvement) were advised to start oral carbamazepine in ascending doses, from daily 100 to 600 mg during 2 months. The results upon tinnitus were again classified in a similar way to that of lidocaine (abolition, improvement, unchanged or worsen).

Results

Regarding gender, there was a significant predominance of females (62.5%), as seen in Figure 1. Tinnitus was classified as severe in 14 cases, as moderate in 8 cases and as mild in 2 cases (Figure 2). According to the time of tinnitus onset, 15 patients had it for less than 2 years, while 3 had it for more than 5 years. There was no significant difference regarding the side of tinnitus (right ear in 54% and left ear in 46%) nor for the number of sounds (single in 54% and multiple in 46%).

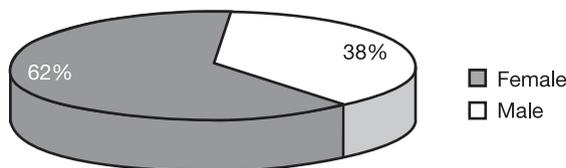


Figure 1 Distribution of patients according to gender.

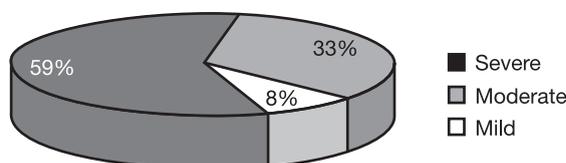


Figure 2 Distribution of patients according to tinnitus severity.

After the administration of the lidocaine, 6 patients referred abolition of their tinnitus, 14 referred improvement, 2 stayed unchanged and 2 worsened (Figure 3). Thus, positive results (abolition + improvement) were noticed in 20 patients. When analyzed according to the severity of the symptom, these positive results occurred in 12 out of the 14 patients with severe tinnitus (85.7%) and in 7 out of the 8 patients with moderate tinnitus (88.8%), as seen in Figure 4.



Figure 3 Effect of the lidocaine test on 24 patients with tinnitus due to sudden deafness.

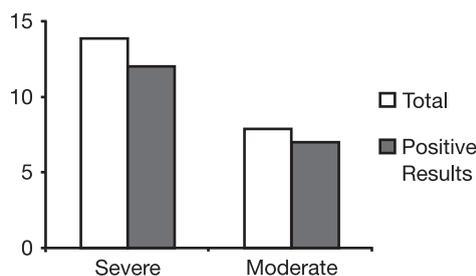


Figure 4 Rate of positive results of the lidocaine test on severe and moderate moderate tinnitus due to sudden deafness.

In relation to the use of oral carbamazepine, 5 of the 6 patients with temporary abolition of tinnitus agreed to use the drug, as well as 12 of the 14 cases with temporary improvement. There was a long-term improvement of the tinnitus in 4 patients (80%) of the first group and in 7 patients from the second group (58.3%), as seen in Figure 5.

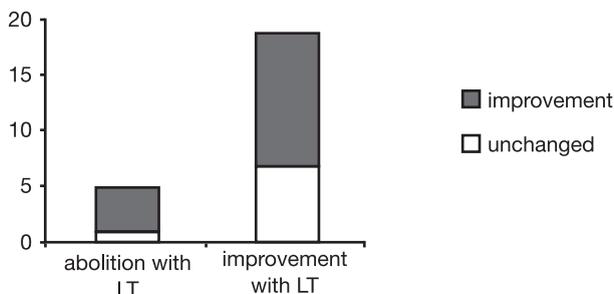


Figure 5 Effect of the long-term treatment with carbamazepine on patients with positive results in the lidocaine test (LT).

Discussion

Tinnitus was classified as severe in 58.3%, as moderate in 33.3% and as mild in only 8.3%. These data allow us to evaluate the importance that tinnitus acquires in patient's daily life, which fully justifies our concern in approaching tinnitus as early as possible. It is not uncommon the patient asking "How long my tinnitus will last until disappear?" with no mention to his hearing loss.

We didn't observe any relation between the response to the lidocaine test and the recovery of the hearing thresholds after the treatment of the

"acute phase" of sudden deafness. Some patients with hearing improvement didn't have positive results to the test, while other patients with profound sensorineural hearing loss had abolition of the tinnitus.

Our results demonstrate effectiveness of the lidocaine test in controlling tinnitus in 83.3% of the cases of sudden deafness. The response was even better in the cases of moderate and severe tinnitus (88.8% and 85.7% respectively). These observations are exciting, once the positivity of the test was higher in patients with sudden deafness than it was in our previous study with tinnitus of varied etiologies [6]. This possibly means a favorable prognostic to the oral use of the carbamazepine and opens a new perspective in the treatment of tinnitus due to this specific etiology, which is one of the most difficult ones to manage.

The oral carbamazepine as a long-term treatment was effective in 64.7% of the patients with positive results to the lidocaine test, sensibly higher than the 50% observed in patients with different etiologies [6]. The average dosage needed to stabilize the improvement of tinnitus was 400 mg/day. Seven patients presented side effects as sedation, dizziness and migraine, evoking an automatic withdrawal of the drug by the patients. We didn't observe direct relationship between the dose of the carbamazepine and the collateral effects, suggesting an individual sensibility in each case.

The lidocaine test should be accomplished in the patient as soon as he refers the appearance of the tinnitus, which in our clinical experience occurs immediately or a few days after the installation of the sudden deafness. Our results are exciting and lead us to question the worth of the precocious institution of such test in order to prioritize the tinnitus management as much as that of the hearing loss.

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Lidocaine test: Effect in patients with tinnitus and relation to the treatment with carbamazepine

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Objectives: There is strong evidence in the literature about the effect of local anesthetics such as lidocaine in order to control tinnitus. These agents act by stabilizing the membrane of hair cells and cochlear nerve fibers. However, the effect of intravenous lidocaine is transient, and its oral analogues did not present the same efficacy for long-term treatment in patients with tinnitus. Some oral anti-epileptic drugs, as carbamazepine, have been used alternatively in several studies. The aim of this work is to evaluate the response to intravenous lidocaine in patients with intractable tinnitus and the effect of oral carbamazepine as a substitute for long-term maintenance of tinnitus relief.

Methods: We studied prospectively 50 patients (28 females and 22 males; mean age 50.9 years) who underwent the lidocaine test, performed by a 3-minute intravenous infusion of 2% lidocaine chlorid-rate. The patients who experienced any relief after the test started using oral carbamazepine in ascending dosages (50–600 mg/day) for 3 months.

Results: The results were classified in tinnitus abolition (18%); marked relief (32%); partial relief (26%); unchanged (22%) and worsening (2%). The lidocaine test showed favorable results (abolition + improvement) in 76% of patients, especially those with bilateral tinnitus ($p < 0.001$). Afterwards, 50% of patients treated with oral carbamazepine maintained the improvement of tinnitus ($p < 0.01$).

Conclusions: The intravenous lidocaine is effective in reducing intractable tinnitus and there is close association between lidocaine and oral carbamazepine effects. Therefore, carbamazepine can be used as a long-term treatment for tinnitus when the patient achieves improvement of symptom after the lidocaine test.

Introduction

The suppressive effect of local anesthetics on tinnitus was discovered casually by Bárány in 1935. During a turbinate infiltration with procaine, the patient spontaneously noted the relief of his tinnitus [1]. Since then, there have been a large number of authoritative studies devoted to the effect of intravenous local anesthetics (especially lidocaine) on tinnitus [2–7]. Engleson demonstrated the accumulation of ^{14}C -labelled lidocaine in the cochlear modiulus after intravenous injection in an experiment with guinea pigs, showing the direct action of the drug in the inner ear [8].

Tinnitus is attributable to an abnormal neuronal activity in the auditory pathways. One current explanation is the functional alteration of ion channels of outer and inner hair cells membrane, with blockage of the lateral potassium channels and leak-

age of sodium through apical membrane channels [9]. This leads to modification of electrochemical gradients throughout the cellular membrane impairing the cochlear electromechanical transduction [10]. It is also supposed that there is an overshoot in the cochlear nerve fibers [11].

Considering these pathophysiological models, as well as the membrane stabilizing effect of local anesthetics, lidocaine might reduce the spontaneous cochlear activity and modulate neural transmission in patients with tinnitus [12]. In fact, recent studies with the patch-clamp technique suggest that lidocaine acts in a dose-dependent manner on outer hair cells calcium-activated potassium channels [13]. In the cochlear nerve it is presumed that lidocaine inhibits the influx of sodium into the neurons via blockage of these ion channels in the internal face of the cellular membrane [13].

The effect of intravenous lidocaine on tinnitus is transient though, and side effects in high doses are noteworthy. Tocainide, its structural analog for oral administration, presented serious toxic effects in a considerable number of patients and quite variable effectiveness [14]. Several clinical studies were car-

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ried out in order to evaluate the help of anti-epileptic drugs in the management of tinnitus. Although its mechanism of action is different from that of local anesthetics, anti-epileptic drugs also can inhibit the hyperactivity of the auditory pathways, with the advantage of being available for oral use with fewer side effects than those of tocainide [4].

Considering the multiple aspects involved in the generation and perception of tinnitus (its characteristics, etiology and onset), which may influence the response to lidocaine test and to the treatment with anti-epileptic drugs, researchers have been trying to identify which patients could be benefited with those medications. The question is whether or not the carbamazepine is able to allow a tinnitus relief similar to that obtained with the intravenous lidocaine, which has an "anticonvulsant-like effect".

The objectives of this study were: (a) analyze the effect of intravenous lidocaine in 50 patients with intractable tinnitus, identifying associations between the responses to this test and some characteristics of tinnitus (onset, type, site and etiology) and (b) evaluate the effect of an oral anti-epileptic drug (carbamazepine) as a long-term management in patients who had improvement of tinnitus after the lidocaine test.

Methods

We studied 50 tinnitus patients unsuccessfully submitted to previous treatments. There were 28 females and 22 males, whose ages ranged between 28 and 78 years (average 50.94 years). According to an analog-visual scale from 1 to 10 for evaluation of the interference of tinnitus in their daily life, 38% of patients were classified as severe tinnitus (scores 8 to 10); 46% as moderate tinnitus (scores 4 to 7); 8% as mild tinnitus (scores 1 to 3) and 8% did not answer.

The following tinnitus data were analyzed for each patient: (a) onset (distributed in: <1 year;

1y-1y11m; 2y-4y11m; ≥ 5 years); (b) site of perception (ear or head; uni- or bilateral); (c) number (single or multiple); (d) etiology (inner or middle ear disease, central nervous system disorder or idiopathic tinnitus).

The lidocaine test was performed through IV infusion of 1mg/kg of 2% lidocaine chloridrate in 3 minutes. According to the results, patients were divided in five groups: (1) abolition of tinnitus; (2) marked relief; (3) partial relief (4) unchanged and (5) worsening. The cases with positive response to the lidocaine test (abolition, marked relief or partial relief) started treatment with oral carbamazepine in ascending dosages from 50 to 600 mg/day during a maximum period of 3 months. The results obtained after the treatment with carbamazepine were prospectively classified in five categories: (1) abolition of tinnitus; (2) improvement; (3) unchanged; (4) worsening and (5) withdrawal.

The results were analyzed by the Fisher, Freeman and Halton, as well as Chi-square tests.

Results

Result of lidocaine test according to the patient (Figure 1). 38 patients (76%) had positive response to the lidocaine test, that is, abolition, marked or partial relief of tinnitus, being referred to the treatment with carbamazepine. Abolition of the symptom occurred in 4 cases of severe tinnitus (21%), 4 of moderate tinnitus (17%) and 1 of mild tinnitus (25%).

Association between the response to the lidocaine test and onset of tinnitus. Considering the 38 patients with positive response to the test, 24 (63.1%) had presented tinnitus for more than 2 years. Ninety percent of the patients with tinnitus in the interval 1 year - 1y11 m had improvement of the symptom, as well as 87% of the patients who had presented tinnitus for more than 5 years. There was no association between the onset of tinnitus and the response ($p = 0.73$).

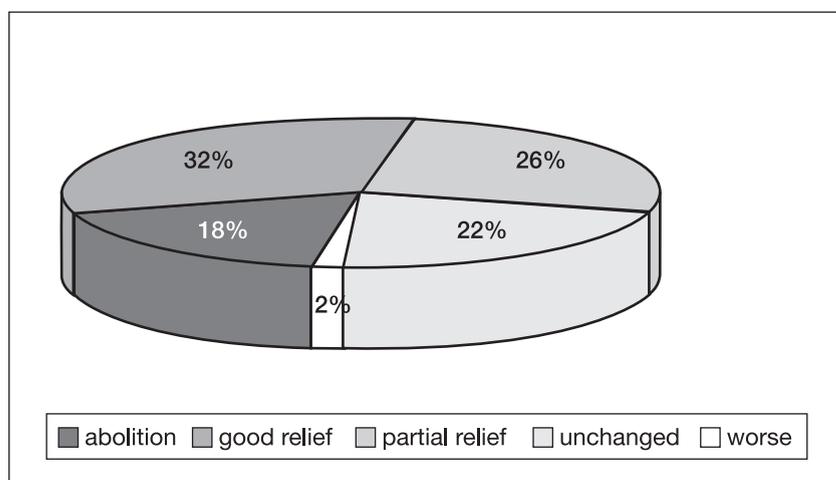


Figure 1 Response to lidocaine test in a group of 50 patients with tinnitus.

Association between the response to the lidocaine test and site of tinnitus. Among patients with favorable responses, 44.7% had unilateral tinnitus, 36.8% bilateral tinnitus and 18.5% perceived the sound in their heads. However, patients with bilateral tinnitus had a significantly better response to the test ($p < 0.001$).

Association between the response to the lidocaine test and number of tinnitus. Among patients with positive results, 55.2% had single tinnitus and 44.8% multiple sounds, with no significant differences ($p = 0.246$).

Association between the response to the lidocaine test and tinnitus etiology. Among 38 patients with tinnitus due to inner ear disorders (metabolic, infectious diseases, presbycusis, ototoxicity and sudden deafness), 27 (71%) had favorable response to the lidocaine test. There were positive results also in all 5 patients with middle ear diseases (otosclerosis and chronic otitis media) and in 3 patients with idiopathic tinnitus. Three out of the four patients with central nervous system disorders (Lyme disease, multiple sclerosis and neurocysticercosis) had improvement of tinnitus (Fig. 5). There was no association between the etiology of tinnitus and the results; however, considering only the patients with inner ear disease, there was a significant prevalence of positive results in this particular group ($X^2 = 5.92$).

Effect of oral carbamazepine on tinnitus. Among 38 patients with positive response to the lidocaine test, 34 underwent treatment with carbamazepine. After this, 17 patients (50%) improved, 10 (29.4%) remained unchanged, 2 (5.8%) worsened and 5 (14.7%) withdrew treatment due to side effects (Fig. 6).

Association between the result of lidocaine test and response to the treatment with carbamazepine (Figure 2). Considering the 9 patients with abolition of tinnitus after lidocaine test, 4 (44.4%) main-

tained the tinnitus lower (although present), and 3 (33.3%) did not notice difference in the symptom. Carbamazepine was never able to promote abolition of tinnitus in our cases, even in those who presented abolition with lidocaine. Considering 15 patients with marked relief of tinnitus after lidocaine, 11 (73.3%) also had improvement with carbamazepine and 2 (13.3%) did not notice improvement (Fig. 7). The association between the results to lidocaine and carbamazepine was significant ($p = 0.0034$).

Discussion and Conclusions

In agreement with previous studies, we found 76% of positive response to the lidocaine test with total or partial relief of tinnitus [6,15,16]. We are partial to the idea that some patients have not presented any relief (or even worsening) of tinnitus because of an individual variation in the lidocaine pharmacokinetics, as proposed by den Hartigh [6]. Maybe these patients did not had enough lidocaine plasma concentration that could influence tinnitus; the plasma concentration of lidocaine that causes reduction of tinnitus is between 1.5 and 2.5 mcg/ml [6]. However, higher serum levels are associated to more pronounced side effects. A recent attempt of using lidocaine with fewer toxic effects is the intratympanic instillation of the drug via ventilation tubes. Having low molecular weight, lidocaine easily crosses the round window towards the inner ear; on the other hand, some patients complain about vertigo during the instillation [13].

Considering the onset of tinnitus, 63.1% of patients with relief of the symptom after the lidocaine test had presented it for more than 2 years. We noticed that 90% of patients with tinnitus between 1 year and 1y11m and 87.5% of those with tinnitus for more than 5 years experienced relief, confirming the tendency of favorable response in cases of chronic tinnitus [14]. Among the patients with intractable tinnitus in our series, we observed just 7

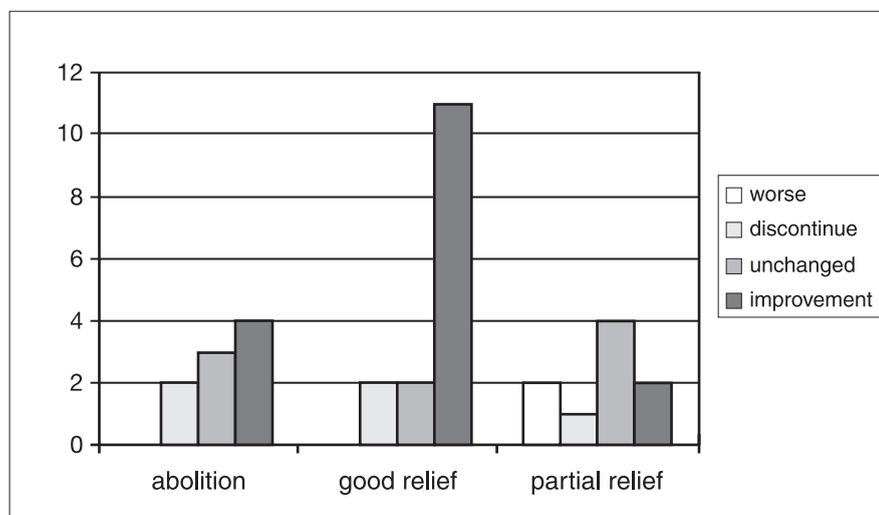


Figure 2 Association between the response to the lidocaine test and results of treatment with oral carbamazepine.

cases of tinnitus for less than 1 year; nevertheless, we found 3 cases of abolition of tinnitus in those patients. We can conclude that therapy with local anesthetics may represent a major accomplishment in management of acute tinnitus.

Lidocaine has been significantly effective in controlling bilateral tinnitus, indicating that the site of tinnitus may exert some influence on its response. We did not come across literature data that might suggest an explanation for this finding. On the contrary, we did not find interference of the number of tinnitus in the response to lidocaine test, with relief in 55.2% of patients with single tinnitus and 44.8% with multiple tinnitus.

There is not definitive evidence of a preferential site of action of lidocaine. According to Martin, it is suggested that lidocaine is more effective in peripheral lesions [15]. On the other hand, Ueda demonstrated an effectiveness of 60.2% (118/196 ears) without significant difference between inner ear or central nervous system disorders [5]. In the current study, the improvement obtained with lidocaine was similar in peripheral and central tinnitus (77.4% and 75%). We also treated five patients with tinnitus associated to middle ear diseases (otosclerosis and chronic otitis media), and all mentioned improvement of their symptom. Despite the small number, we wish to highlight the future possibility of using this therapy to control tinnitus in patients who cannot or do not want to be submitted to a middle ear surgery, such as stapedotomy or tympanoplasty. Indeed, the authors are already carrying out a complete study to check this possibility.

Literature shows that the effect of lidocaine on tinnitus may be influenced by several factors: etiology of tinnitus [2], association to hearing loss [4] and drug plasma level [17]. Bearing in mind our results and knowing that tinnitus is a symptom, not a disease, we believe that this diversity is expected, reinforcing the need for exhaustive studies so as to confirm which group of patients with tinnitus may be benefited with the lidocaine test.

The positive response to the lidocaine test had a quite good association with results of carbamazepine therapy, and 50% of patients that had had relief of tinnitus with the former also had improvement with the latter. Our data agree with the report of Viada, whose study demonstrated a curious paradox: in spite of 44% improvement registered by patients after oral carbamazepine, the loudness and pitch matching test has shown improvement in 77.7% of cases [18]. Probably, in order to be noticed, the improvement has to reach some "degree of significance" to the patients.

The best association between the response to the lidocaine test and to oral carbamazepine occurred in patients with marked relief of tinnitus after the test; this group also presented a significant relief of their symptom with the anti-epileptic drug. The limit for the use of carbamazepine were the appearance of side effects, as sedation, vertigo, migraine, and skin rash. Therefore, taking into account the risks and benefits of the treatment with

carbamazepine, we conclude that this drug should be used only in cases which present relief of tinnitus after the lidocaine test. Nevertheless, the improvement obtained with lidocaine may not be reached with the anti-epileptic drug. Newer anti-epileptics such as lamotrigine, vigabatrin, gabapentin and felbamate may be alternatives in the treatment for tinnitus, with fewer side effects than the older ones.

The present study demonstrated that the lidocaine test can be performed in all patients with intractable tinnitus, regardless its etiology, unless there is a formal medical contra-indication. The response should be interpreted in its subtleties, and long-term therapy with anti-epileptic drugs should be started only after a thorough exam.

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Study of the occurrence and the characteristics of tinnitus in a Brazilian audiological clinic

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The aim of this study was to investigate the occurrence of tinnitus in a six month sampling of patients attended in an audiological clinic in São Paulo, Brazil. We also examined the lateralization of tinnitus, the type of hearing loss, if present, the audiometric configuration and its relation with tinnitus. Of the 406 patients evaluated in that period, 233 (58%) presented tinnitus complaint. Out of these, 158 (68%) were female and 75 (32%) were male. Their ages ranged from 5 to 92 years old. It was more frequent in women (69%) with ages between 55 and 75 years old. The most frequent audiometric finding was descendent (64.5%) sensorineural hearing loss (55%). It is important to emphasise that we found a high number of people (27%) who present tinnitus complaint but have normal hearing.

Introduction

Tinnitus is one of the leading complaints in ENT and Audiological clinic. According to the American Tinnitus Association, it is estimated that about 50 million American adults report some sort of tinnitus. Out of that, 12 million people feel the necessity to search for professional help.

A Brazilian study [1] established that tinnitus was the main complaint in 50% of the people attended in an ENT clinic.

Tinnitus can be defined as an audible sensation that cannot be consciously attributed to any external source, or to 'sounds originated outside the body' [2].

Tinnitus sufferers usually associate them to negative changes in their life quality. They complain about irritability, concentration difficulties, sleep disorders, health problems, difficulty in understanding speech, and further problems. Tinnitus may be a source of intense anxiety leading sometimes to depression and, in some severe cases, to suicide.

The aim of this study was to investigate the occurrence of tinnitus in a six month sampling of patients attended in an audiological clinic in the city of São Paulo, Brazil. We further examined the

lateralization tinnitus, the type of hearing loss, if present, the audiometric configuration and its relation with tinnitus.

Method

We analysed the medical data of 406 patients attended in an audiological clinic located in São Paulo, Brazil, in a 6 month period. Of these, we report data on of patients with tinnitus complaint.

All the subjects were submitted to anamnesis, pure tone audiometry for 0.25, 5, 1k, 2k, 3k, 4k, 6k, 8k Hz (air and bone conduction), speech audiometry (Speech recognition threshold and Speech recognition Index), middle ear function analysis (tympanometry and acoustic reflex).

We investigated the lateralization of tinnitus (if bilateral, unilateral or central), the type of hearing loss (normal, sensorineural, sensorineural with high frequency loss, conductive or mixed), the audiometric configuration (flat, descendent, ascendent, U-type), and their relation with the symptom.

Results

Out of the 233 (58%) who presented tinnitus complaint, 158 (68%) were female and 75 (32%) were male.

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The ages of the tinnitus patients varied from 5 to 92 years old and, tinnitus incidence was higher in subjects with ages between 55 and 75 years old.

One hundred and thirty eight (60%) of the subjects reported bilateral tinnitus, 85 (36%) unilateral and 10 (4%) central.

Out of 466 evaluated ears, 256 (55%) presented sensorineural hearing loss, 129 (27%) normal hearing, 50 (11%) high frequency hearing loss, 19 (4%) mixed and 13 (3%) conductive hearing loss.

In relation to audiometric configuration, out of the 466 evaluated ears, 300 (64%) presented descendent audiogram, 148 (31.7%) flat, 8 (1.7%) ski shape, 6 (1.3%) U shape and 4 (0.8%) ascendent .

Discussion and conclusion

The incidence of tinnitus in developed countries has been reported at around 20 to 30% of the population [3,4,5].

Our study showed an incidence of tinnitus significantly higher than this, in agreement with another Brazilian report of almost 50% [1]. We think this difference is a consequence of the methodology adopted. We analysed tinnitus occurrence in a clinical routine population, whereas the studies cited above investigated the complaint among over-all population.

In relation to gender, our study is in agreement with literature [6,7,8], although these studies did not show statistical significance. We found a higher incidence of tinnitus complaint in female subjects (69%).

We observed that tinnitus was more frequent among individuals whose ages ranged from 55 and 75 years old. Researchers also reported a higher occurrence of tinnitus complaint in senior citizens [7,8,9,10]. Maybe the ageing process of the structures responsible for nutrition may provoke a change in the inhibitory function of the nervous structures responsible for the triggering and synchronicity of spontaneous activity. The spontaneous activity of nervous auditory system is inaudible. The auditory nervous fibers trigger in an independent way and if they fail in the production of synchronous triggers this could be enough to activate certain cochlear nucleus cells. These changes on the stimuli produced may be audible in such a way that the adjacent nervous fibers begin to trigger more synchronously with the stimuli than the responsible fibers. This means that these triggers become correlated to the produced stimuli [11].

Our results showed a higher occurrence of bilateral tinnitus than unilateral or central perception. Some reports confirmed these results [12,13,14] and others found higher incidence of unilateral tinnitus [1,8].

We believe that people who report central tinnitus may be bilateral sufferers who have difficulty to localise tinnitus in a correct way. The correlation

between tinnitus and neural activity emphasises the fact that any activity that happens at any level in the central auditory nervous system will increase the activity on higher centers [11]. We know that beyond the superior olivary complex, hearing begins to have a binaural representation.

Tinnitus complaint was higher in subjects who presented sensorineural hearing loss than in the normal hearing group. The number of people with normal hearing and tinnitus was astonishingly high. These data agreed with other Brazilian studies [1,10] and led us to question if tinnitus may be an indicator factor of a hearing problem or of an otologic disease.

Some classical texts on medical studies report tinnitus as a symptom of some disorders that may affect the ear (e.g. otosclerosis, labyrinthine hydrops, noise induced hearing loss). If tinnitus is an indicator of pathology, how to act with a person who presents tinnitus but does not develop any other disease? Are the organic factors responsible for the tinnitus origin?

There are many subjects who refer that their tinnitus gets worse when they are in a stress situation, or living a moment of tension. Others refer that tinnitus gets worse when they drink alcoholic beverages or when they smoke too much. The main question is if it is possible to say that tinnitus is a neuropsychologic symptom or that it has an organic basis. Some studies made with images taken by PET SCAN, showed that tinnitus modifies the cerebral activity out of the auditory primary area [15].

No report about the relationship between the audiometric configuration and the presence of tinnitus could be found. We believe that our findings about a higher occurrence of tinnitus complaint in subjects with descendent audiograms may be due to the age of the studied population, over to 55 years old.

The analysis of the results led us to conclude that:

- 1 Tinnitus complaint was present in 58% of the studied population;
- 2 Tinnitus was more frequent in women (69%) with ages between 55 and 75 years old;
- 3 The most frequent audiometric finding in those patients with tinnitus was descendent (64.5%) sensorineural hearing loss (55%);
- 4 It is important to emphasise that we found a high incidence of people (27%) with tinnitus complaint but otherwise normal hearing.

Since tinnitus is a very common complaint and, as our knowledge about it is not complete, we observe that for the physician, for the audiologist and for the patient it is a very hard symptom to deal with.

It is important to channel our energy and knowledge towards finding new approaches or new rehabilitation programs, that may be more efficient and may improve the life quality of tinnitus sufferers.

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Improvements in tinnitus severity: A follow-up study

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Introduction: Few studies have assessed the *long-term* effects of treatment programs on specific measures of tinnitus severity and loudness. Follow-up questionnaires were used in the present study to assess these factors in patients one to four years after they completed a comprehensive tinnitus treatment program.

Methods: One hundred seventy four patients (130 males, 44 females; mean age 55.9 ± 11.6 years) who attended our tinnitus clinic between 1994–1997 rated the loudness of their tinnitus and answered twelve questions relating to tinnitus severity before and one to four years after initiation of their treatment program. Every treatment program included patient education, counseling, and reassurance. In addition, some patients also received acoustic therapy, medication, or recommendations for medical intervention or psychotherapy.

Results: There was no significant change in self-rated loudness of tinnitus. However, there was significant improvement in nine of the twelve measures of tinnitus severity for the entire patient population. A subset of 40 patients who purchased and used in-the-ear devices (hearing aids, maskers, or combination instruments) reported significant improvement in all twelve measures of tinnitus severity.

Conclusion: Individualized, comprehensive treatment programs can facilitate long-term improvements in tinnitus severity.

Introduction

Innumerable treatments for chronic tinnitus have been utilized – with varying degrees of success – by clinicians and patients. Many studies have been undertaken to assess the effectiveness of tinnitus treatment programs or methods. However, few studies of the efficacy of tinnitus treatments have assessed their longer-term effects on tinnitus severity. This is an important point to consider because the patients' perception of their tinnitus can change with time. The present study was designed to assess tinnitus severity in patients one to four years after they completed a comprehensive treatment program.

Methods

Detailed questionnaires were mailed to patients prior to their initial appointment at the Oregon Health Sciences University Tinnitus Clinic between

1994–1997. These questionnaires requested information about patients' medical, hearing, and tinnitus histories. The initial appointment at the clinic had the following format – many of these procedures were described by Johnson [1]: (1) Patients met with staff members for an in-depth interview and review of their medical, hearing, tinnitus, and psychosocial histories and conditions; (2) Audiological evaluations; (3) Tinnitus evaluations; (4) Evaluations of acoustic therapies; (5) Review of the results of evaluations; presentation of treatment plan and other recommendations.

Follow-up questionnaires were mailed to the same patients one to four years (mean = 2.30 ± 0.76 years) after their initial appointment. Table 1 contains the follow-up questions. These questions were also asked in the initial questionnaires. Questions 1–12 constitute the Tinnitus Severity Index [2–3] which is an efficient indicator of the negative impacts of tinnitus upon patients. The rating scale for these questions can be found in this volume within our paper entitled "Effects of insomnia on tinnitus severity: a follow-up study." Data relating to patient demographics, audiometric thresholds, tinnitus loudness, and tinnitus severity were analyzed for patients who returned follow-up questionnaires.

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Results

One hundred seventy four patients (130 males, 44 females; mean age = 53.6 ± 11.6 years at the time of their initial clinic appointment) returned follow-up questionnaires. The age range for these patients at the time of their initial visit to the Clinic was 17 to 83 years. The age range for patients who returned follow-up questionnaires was 20 to 85 years (their mean age increased to 55.9 ± 11.6 years).

Table 1 contains the means, standard deviations, and statistical comparisons (paired, two-tailed t-tests) of patients' ratings of the loudness of their tinnitus on the initial and follow-up questionnaires. Even though there is a slight decrease in tinnitus loudness reported on the follow-up questionnaire, this difference is not statistically significant ($p = 0.117$).

Table 1 also contains the means, standard deviations, and statistical comparisons of patients' responses to the twelve questions relating to tinnitus severity. A repeated measures multivariate analysis of variance was performed on these data to control for the number of comparisons as well as for the fact that the same subjects responded to both the initial and follow-up questions. The overall Wilks' Lambda F value was calculated to be 4.39 with $p < 0.0005$. This indicated that there was a significant change in responses on the follow-up questionnaire and allowed us to proceed with univariate tests. P values resulting from univariate comparisons of initial and follow-up responses to each of the twelve severity questions are listed in Table 1. Using an alpha of 0.05, the Bonferroni correction produced a significance level of 0.004 for each of these items.

On the follow-up questionnaire, patients in the present study reported improvement in all twelve of the tinnitus severity questions. According to the

statistical criteria outlined in the previous paragraph, patients reported *significant* improvement in nine of these items.

Nineteen patients improved their sleep patterns from the time of the initial to the follow-up questionnaires. On the follow-up questionnaire, these patients also reported significant improvements in all eleven of the other questions relating to tinnitus severity.

Discussion

Patients in the present study reported significant improvements in most of the specific measures of tinnitus severity one to four years after receiving treatment at our clinic. However, there was no significant change in reported loudness of tinnitus from the time of the initial to the follow-up questionnaires. The fact that the reported loudness of tinnitus was not correlated with changes in its severity is in agreement with observations made by Meikle *et al.* [4] and should be considered when assessing patients or prescribing treatments. Patients' ratings of the loudness of their tinnitus are not necessarily good indicators of the severity of their condition.

What was responsible for the significant improvements in tinnitus severity reported by patients in the present study? Because the treatment programs at our clinic are multidimensional and designed for each patient according to his or her personal and medical histories and conditions, it is impossible to identify one procedure or treatment that was primarily responsible for the overall improvement of the group. However, a combination of the following recommendations and treatments contributed to the improvements in tinnitus severity reported by our patients:

Table 1 Responses to questionnaires

| | Initial | Follow-up | $p \leq$ |
|--|-----------------|-----------------|----------|
| Loudness of tinnitus on a 1-to-10 scale | 6.69 ± 2.02 | 6.42 ± 2.18 | 0.117 |
| Does your tinnitus . . . | | | |
| 1 Make you feel irritable or nervous? | 3.27 ± 0.97 | 2.88 ± 0.87 | 0.0005 |
| 2 Make you feel tired or stressed? | 3.25 ± 1.13 | 2.91 ± 0.95 | 0.0005 |
| 3 Make it difficult for you to relax? | 3.37 ± 1.03 | 3.06 ± 1.01 | 0.0005 |
| 4 Make it uncomfortable to be in a quiet room? | 3.43 ± 1.24 | 3.31 ± 1.26 | 0.164 |
| 5 Make it difficult to concentrate? | 3.30 ± 1.05 | 3.03 ± 0.97 | 0.001 |
| 6 Make it harder to interact pleasantly? | 2.97 ± 1.11 | 2.74 ± 0.96 | 0.014 |
| 7 Interfere with required activities? | 2.86 ± 1.21 | 2.59 ± 1.03 | 0.004 |
| 8 Interfere with social activities? | 3.01 ± 1.20 | 2.82 ± 1.06 | 0.062 |
| 9 Interfere with overall enjoyment of life? | 3.37 ± 1.10 | 3.12 ± 1.10 | 0.004 |
| 10 Interfere with sleep? | 2.11 ± 0.77 | 1.90 ± 0.77 | 0.0005 |
| 11 How much effort is it to ignore tinnitus? | 2.83 ± 0.98 | 2.47 ± 0.91 | 0.0005 |
| 12 How much discomfort do you usually experience when tinnitus is present? | 2.86 ± 1.00 | 2.50 ± 0.92 | 0.0005 |

(1) *Patient education, reassurance, and demystification of tinnitus*

(2) *Acoustic therapy*: In the present study, 40 patients purchased hearing aids, ear maskers (a.k.a. sound generators), or tinnitus instruments (combinations of hearing aids + ear maskers) based on recommendations they received during their initial clinic appointment. On the follow-up questionnaire, this group of patients reported significant improvement on all twelve of the questions relating to tinnitus severity. In addition to in-the-ear devices, many patients also added sounds to their work or home environments by using a radio, television, tapes, CDs, tabletop sound generation machines, electric fans, or portable fountains.

(3) *Medications*: One factor that contributes to increased tinnitus severity is insomnia [5,6]. Patients with severe insomnia were advised to talk with their physicians about prescription medications to improve their sleep patterns.

Improvements in sleep patterns experienced by patients in the present study are attributable to several factors: medications; additions of environmental sounds; reduced anxiety; improved coping strategies, attention-switching, and relaxation techniques; and psychological counseling. The fact that improvements in sleep interference contributed to improvements in overall ratings of tinnitus severity underscores the importance of identification and effective treatment of insomnia for patients with tinnitus.

Anxiety [7,8] and depression [9,10] can also contribute to increased tinnitus severity. Treating these disorders with appropriate medication in conjunction with psychological counseling can also reduce tinnitus severity for many patients.

(4) *Psychological counseling*: Some directive counseling occurred during the initial clinic visit including advice about relaxation and attention-switching techniques, and identification of problems that might require longer-term therapy (including insomnia, depression, anxiety, stress or anger management, and obsessive-compulsive disorders). Patients who would benefit from ongoing psychotherapy were referred to psychiatrists, psychologists, or licensed clinical social workers in their area.

(5) *Follow-up*: At the conclusion of their initial appointment, patients were encouraged to contact the clinic by telephone or to return for follow-up appointments if they had any additional questions or concerns, or if they required additional information, reassurance, or recommendations.

Conclusions

Individualized treatment programs that were designed for each patient in the present study contributed to the overall improvement in tinnitus severity reported on follow-up questionnaires. Several clinicians agree that a combination of appropriate treatments is more effective than one form of remediation used in isolation [11–13]. Even though

a customized combination of treatments is effective for many patients with chronic and bothersome tinnitus [14], the process can be very time consuming. Most family physicians and otolaryngologists are not able to spend even a small fraction of this much time with one patient during an office visit. If the clinician has assessed and treated every reasonable medical cause for a patient's tinnitus, and the patient reports little improvement in tinnitus severity, the clinician should do one of two things: (1) spend the time necessary to effectively treat the patient according to procedures described here and elsewhere [1,12,14]; or (2) refer the patient to a comprehensive treatment center with experienced personnel who are willing and able to spend a substantial amount of time with each patient. For a certain number of patients with chronic and severe tinnitus, only a specialized treatment program of this type can help them to improve their condition.

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The psychological and psychoacoustical evaluation of tinnitus

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Several methods have been described for tinnitus measurement and outcome evaluation. Many tests have been developed in order to evaluate the impact on their quality of life and subsequently decide the most adequate management approach. Two hundred and fifty-seven patients have been enrolled in our study. We performed our tinnitus protocol in all of them. Correlation tests between psychoacoustical measures (Loudness, MML) and subjective ones (THI; VAS; number of wrong beliefs) showed a very low correlation and a great dispersion. The comparison of subjective measures (THI; VAS) and tinnitus groups according to pitch, type of sound, residual inhibition and sound oversensibility showed significant differences. Exception was confirmed for patients presenting a subjective oversensibility to environmental sounds that showed a high THI scores ($p < 0.001$).

Introduction

The lack of an objective method for tinnitus measurement has made difficult the diagnosis and outcome control of this symptom. The psychoacoustical model attempted to evaluate the audiological features of tinnitus in the late 70's [1]. Loudness and pitch matching, minimal masking levels, total or partial residual inhibition and Feldmann's masking curves [2] were the reference for research validation. Development of neurophysiological model [3,4] has carried out the importance of its effect on patient's life as an outcome measure. Evaluation of stress and anxiety, the use of visual analogical scales of tinnitus loudness and annoyance or the psychological tests are more close to a real evaluation of the clinical effects of tinnitus.

The purpose of this study is to valorate tinnitus measurement according to the two models, as well as to find common relationships between both groups of measures.

Material and Methods

Two hundred and fifty seven patients from our tinnitus clinic have been enrolled in this study. Our tinnitus evaluation protocol includes:

- (1) Psychoacoustical assessment. Pure tone audiometry (hearing loss was considered if 0.5–2 khz average threshold was below 30 dBHL). Loudness and pitch matching of most troublesome tinnitus. Minimal masking level (MML) using narrow band noise (dBHL) and residual inhibition (RI), 10 dBHL over MML. It was considered positive if tinnitus perception was reduced after 1 minute of noise exposition. Uncomfortable loudness levels were evaluated as well (0.25 to 4 Khz).
- (2) Subjective and psychological assessment. Visual analogical scales on tinnitus intensity (0–10), Tinnitus Handicap Inventory [5] (0–100%), number of wrong beliefs associated to tinnitus, according to a list (0–9) and oversensibility to environmental sounds referred by the patient.

Results

Loudness matching average was 9.8 dBHL (± 8.1); the most common pitch group was high frequency one (3–12 Khz), 52.4% of the cases; tinnitus type was more common as a narrow band noise (53%). Hearing loss was evidenced in 54.5% of the patients. Forty-nine percent referred an oversensibility to sounds. MML average was 24.5 dBHL (± 23.7) and a positive residual inhibition was present in 59.9% of the cases.

THI average was 44.2%, analogical scale (VAS) score was 3.6 and the number of wrong beliefs associated to tinnitus was 3.7.

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Table 1 Correlation test between psychoacoustical and subjective measures

| | Loudness | MML | THI | VAS | Wrong beliefs |
|---------------|----------|------|------|------|---------------|
| Loudness | | 0.03 | 0.09 | 0.12 | 0.11 |
| MML | 0.03 | | 0.22 | 0.27 | 0.08 |
| THI | 0.09 | 0.22 | | 0.42 | 0.6 |
| VAS | 0.12 | 0.27 | 0.42 | | 0.32 |
| Wrong beliefs | 0.11 | 0.08 | 0.6 | 0.32 | |
| | | | | | $p < 0.001$ |

Correlation test between psychoacoustical (loudness, MML) and subjective measures (THI, VAS score and number of wrong beliefs) showed a very low correlation with a high dispersion of the values in a graphic representation.

The comparison (ANOVA) of subjective measures (THI, VAS) and tinnitus groups according to pitch, type of sound, residual inhibition and sound oversensibility showed no significant differences. Exception was confirmed for patients presenting a subjective oversensibility to environmental sounds that showed a high THI scores ($p < 0.001$).

Discussion

It has been proved by many authors the low interest of psychoacoustical measurement in tinnitus evaluation. We think they could be important in order to establish a comfortable atmosphere between patient and physician. The absence of any correlation between both groups of measures prove the difference of tinnitus perception and tinnitiuts reaction.

Subjective measurement according to THI and VAS score are not so reliable. They depend on patient's cultural level and the presence of other disabling symptoms (hearing loss, vertigo, hyperacusis). Even though, it is obvious their importance in the assessment of patient's quality of life.

Table 2 Comparison of subjective measures and different tinnitus groups

| Pitch (Hertz) | N = 212 | THI | VAS |
|---------------------|------------|-------------------------|---------------|
| 125–250 | 33 | 41.53 | 6.79 |
| 500–2000 | 69 | 44.25 | 6.59 |
| 3000–12000 | 110 | 46.56 | 6.45 |
| <i>Total</i> | <i>212</i> | <i>45.02</i> | <i>6.55</i> |
| | | <i>No sig</i> | <i>No sig</i> |
| Type of sound | N = 230 | THI | VAS |
| NBN | 122 | 45.24 | 6.58 |
| WTN | 20 | 43.79 | 7.25 |
| PI | 88 | 44.9 | 6.5 |
| <i>Total</i> | <i>230</i> | <i>44.99</i> | <i>6.61</i> |
| | | <i>No sig</i> | <i>No sig</i> |
| Residual inhibition | N = 203 | THI | VAS |
| Positive | 120 | 48.03 | 6.88 |
| Negative | 70 | 42.62 | 6.74 |
| Rebound | 13 | 45.38 | 5.85 |
| <i>Total</i> | <i>203</i> | <i>45.99</i> | <i>6.77</i> |
| | | <i>No sig</i> | <i>No sig</i> |
| Algyacusis | N = 257 | THI | VAS |
| Positive | 127 | 51.02 | 7.08 |
| Negative | 130 | 39.09 | 6.23 |
| <i>Total</i> | <i>257</i> | <i>45.08</i> | <i>6.67</i> |
| | | <i>Sig p < 0.001</i> | <i>No sig</i> |

Conclusion

The low correlation between psychoacoustical and subjective measurement of tinnitus could reflect the variability of tinnitus perception and reaction. Research on its evaluation would increase in the future, the diagnosis and outcome possibilities.

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Clinical course of tinnitus in patients with sudden deafness

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The clinical course of tinnitus was examined in 90 patients with idiopathic sudden deafness (SD) and this was compared with the recovery of hearing. Approximately 50% of patients experienced persistent tinnitus during the first week after the onset of SD and this decreased gradually by approximately 10% beyond the 5th week. In contrast, the proportion of tinnitus-free patients increased from 20 to 40% during the same period. The tinnitus with a pitch matching low frequency or broad band noise was more frequently observed in SD than in other otological diseases. Approximately 60% of our patients experienced a change in pitch or timbre of tinnitus over time. In the groups with a good hearing recovery, decreasing and temporally increasing types of loudness change were predominant, whereas in patients with a poor hearing recovery, fluctuating, constant, and tinnitus-free types were most frequently observed.

Introduction

In acute sensori-neural hearing loss, the characteristics of associated tinnitus can change over time, although the nature of this change has not yet been fully clarified. In the present study, we investigated the course of pitch and loudness of tinnitus in patients with idiopathic sudden deafness (SD) retrospectively, and compared the finding with the recovery of hearing.

Methods

Ninety subjects were selected from those who visited our ENT clinics within 2 weeks after the onset of SD, and were treated and followed for at least 2 weeks from the first visit or until their hearing recovered to the normal level and tinnitus disappeared.

They were classified into 7 types according to the clinical course of tinnitus loudness: tinnitus-free (throughout the course), increasing, temporally increasing, constant, temporally decreasing, decreasing, and fluctuating type. Loudness change of tinnitus were considered significant when the estimated loudness of tinnitus changed by more than 10 dB in effective loudness level [1], or when a change of more than 5 dB induced a subjective

change in loudness in the patient. When loudness matching could not be performed, loudness change of tinnitus was judged subjectively only.

The degree of hearing recovery was classified into 3 categories based on the initial and final audiograms. It was defined as "cure" when hearing threshold levels (HTLs) at 5 frequencies, 250, 500, 1000, 2000, and 4000 Hz were estimated to have recovered to the level before the onset of SD, "partial recovery" when the mean recovery of HTLs at the above 5 frequencies was greater than or equal to 20 dB, and "slight or no recovery" when this value was less than 20 dB.

Results

Incidence

The presence and persistence of tinnitus during different periods after the onset of SD are shown in Figure 1. As shown in the figure, the proportion of patients with persistent tinnitus did not change for the first 3 weeks and then decreased slightly thereafter, whereas those patients who were tinnitus-free increased during the first 3 weeks and then reached a plateau. Throughout the course, 12 patients (13.3%) did not experience any tinnitus, 51 patients (56.7%) experienced intermittent tinnitus, and 27 patients (30.0%) experienced persistent tinnitus. There was no significant correlation between the presence of tinnitus on the day of onset of SD and hearing recovery. Furthermore, only the cure group showed a significant decrease in the incidence of tinnitus at the final visit (Figure 2, $p < 0.005$).

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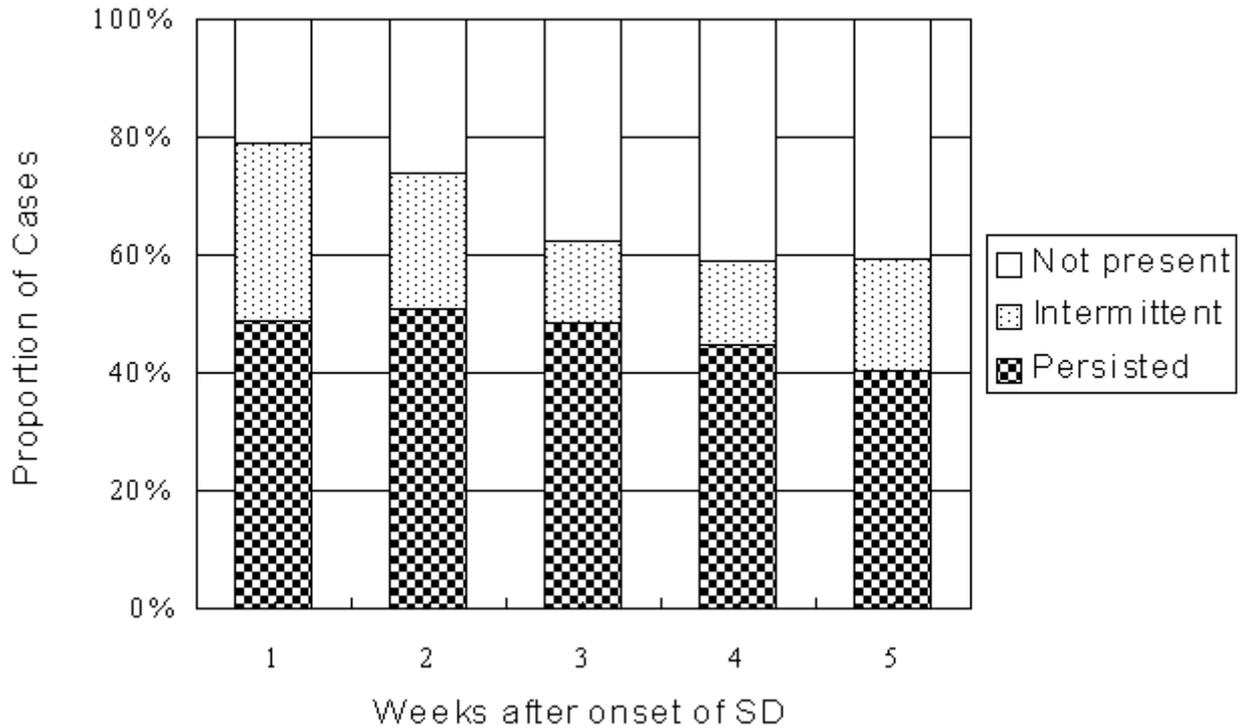


Figure 1 Presence and persistence of tinnitus each week after onset of SD

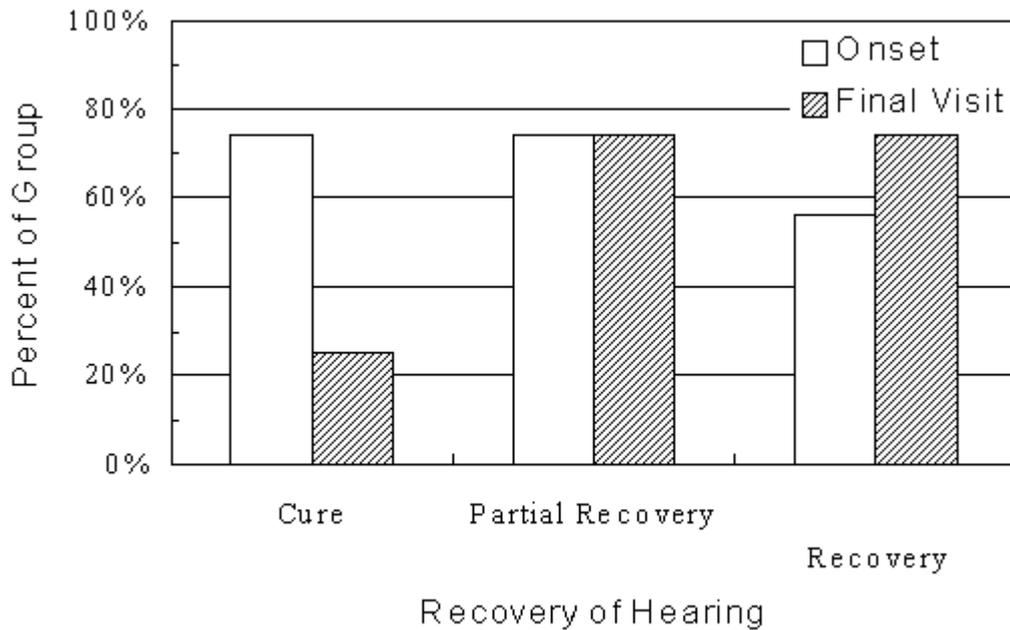


Figure 2 Incidence of tinnitus at onset of SD and final visit in patients with different hearing recovery

Pitch and timbre

In Figure 3, the results of pitch matching are shown for 67 patients. In each case, the pitch of the loudest tinnitus was chosen when multiple tinnitus was experienced. The pitch of the tinnitus was matched to a frequency less than or equal to 1000 Hz in 32 patients (47.8%), greater than 1000 Hz in 26 patients (38.8%), and broad band noise in 9

patients (13.4%), indicating that in SD the percentage of tinnitus with low pitch or like broad band noise is greater than in other otological diseases. Of 77 patients with tinnitus, 46 (59.7%) reported that the pitch or timbre of tinnitus changed. These changes were confirmed by the pitch match test in 36 cases, in which the pitch changed from high to low frequency in 10 cases, from low to high frequency in 1 case, and to both

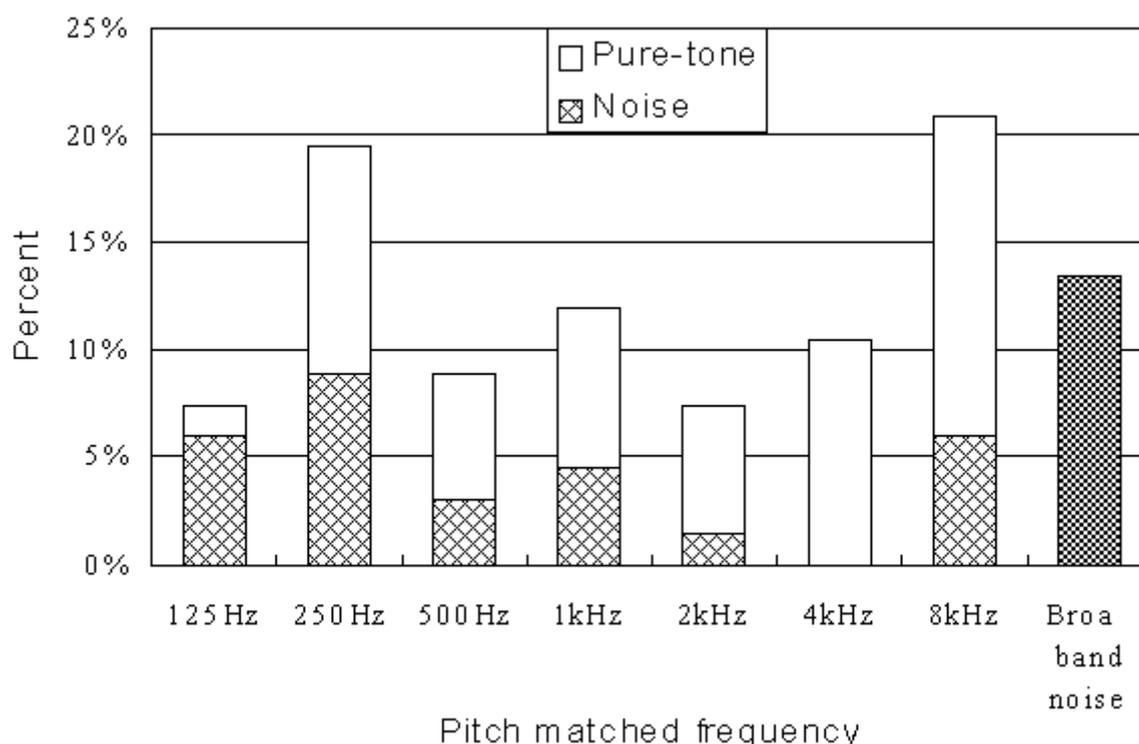


Figure 3 Results of tinnitus pitch matching

directions in 10 cases. Change of timbre (tonal or noise-like) was observed in 17 cases, and band width change (narrow or broad band noise) in 7 cases.

Loudness

Loudness of tinnitus in 55 cases was followed by the balance test. The maximum loudness estimates of

tinnitus throughout the course ranged from 1 to 60 dB in effective loudness level with a median of 18 dB.

Results related to the course of tinnitus loudness and hearing recovery are shown in Table 1, and 4 typical cases of the course of tinnitus loudness and hearing recovery are shown in Figure 4. In the groups with good hearing recovery (cured group), decreasing type and temporally increasing type of

Table 1 Course of tinnitus loudness among patients with different hearing recovery

| Type of tinnitus loudness change | Recovery of hearing | | | Total (n) |
|----------------------------------|---------------------|----------------------|------------------------|-----------|
| | Cure (n) | Partial recovery (n) | Slight/No recovery (n) | |
| Decreasing | 14 | 9 | 1 | 24 |
| Temporally increasing | 9 | 8 | 1 | 18 |
| Fluctuating | 1 | 8 | 8 | 17 |
| Temporally decreasing | 0 | 2 | 4 | 6 |
| Increasing | 0 | 1 | 5 | 6 |
| Constant | 0 | 1 | 6 | 7 |
| Tinnitus-free | 4 | 2 | 6 | 12 |
| Total | 28 | 31 | 31 | 90 |

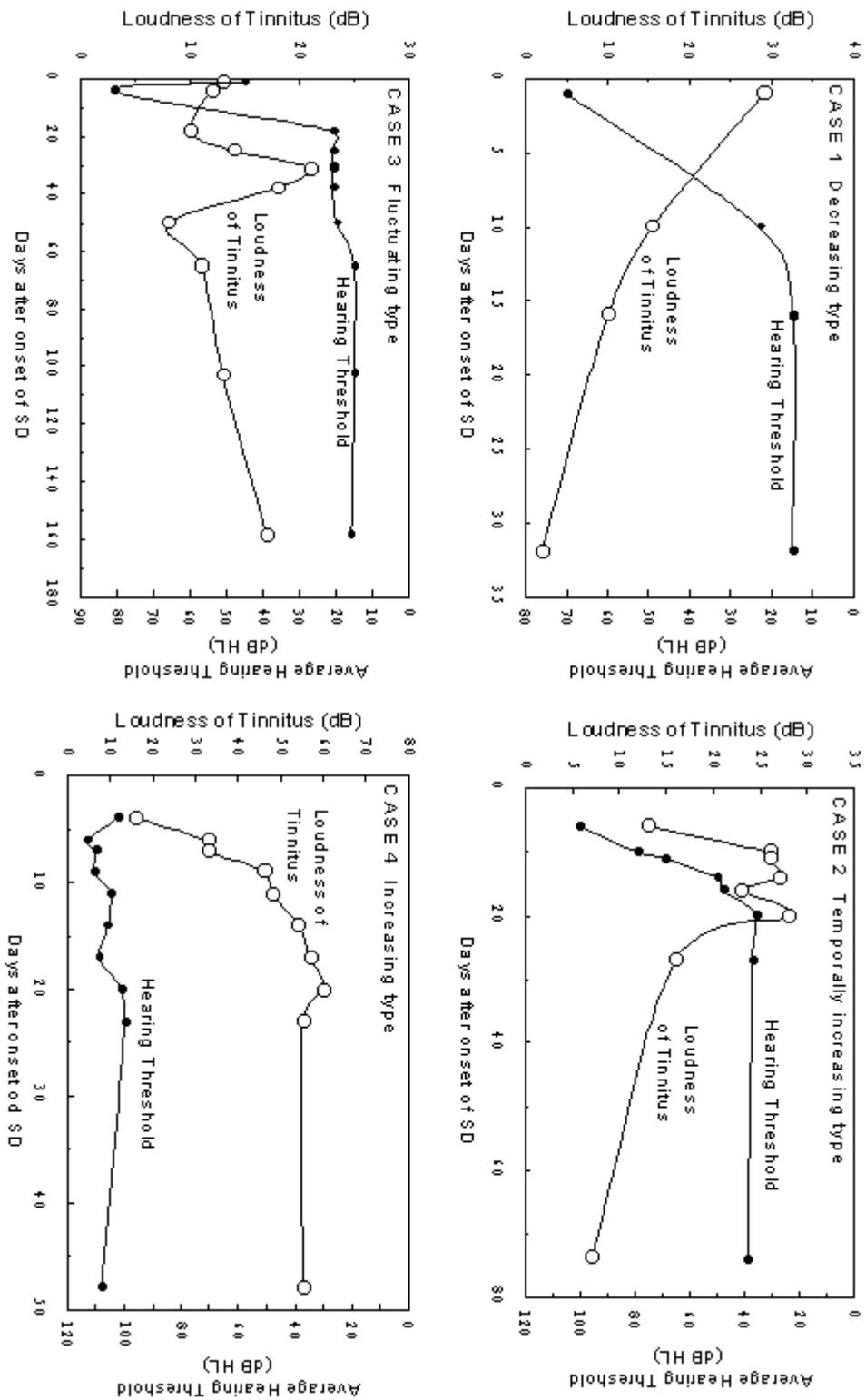


Figure 4 Four typical courses of tinnitus loudness and hearing recovery

tinnitus loudness were the most frequently observed courses, whereas the other types (fluctuating, constant, and tinnitus-free type) were dominant in the poor recovery group. In only 7 cases, tinnitus was present with no change in loudness over time. In 18 cases of temporally increasing type, a median maximum loudness of 27 dB (range 16 to 60 dB) was attained on the 6th day (median value; range 2nd to 33rd day) after the onset of SD, when the average hearing threshold level was a median of 55 dB (range 21 to 98 dB).

Discussion

Due to damage to a large area of the cochlea and extreme changes in the pathological status during the course after the onset of SD, it is not surprising that pitch match frequency of tinnitus was rather evenly distributed in every octave range of frequency and more than half of the subjects experienced changes in pitch and timbre of tinnitus.

These pitch changes may be explained as that many local areas in the cochlea are in a status easily emit-able abnormal spontaneous discharge causing tinnitus if one final condition is added, and the distribution of the area fulfilling this condition changes over time with environmental changes during the recovery course.

In temporally increasing type change of tinnitus, loudness increase was often observed at the stage of rapid hearing recovery. Large number of patients who showed this type of change indicates that there is an optimal condition for the appearance of tinnitus in a certain recovery stage of the pathological condition in the cochlea.

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Katamnesis-study (1 or 2 years after in-patient treatment)

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A post-examination of chronic complex tinnitus patients one to three years after indoor treatment at the Tinnitus-Clinic Arolsen showed clear and stable success judged by the mean global score of the Tinnitus-Questionnaire (German version of the TQ, Goebel and Hiller 1992), that was part of a battery of self-rating questionnaires. Further analysis of the TQ led to the identification of four different groups of patients: stable achievers, late achievers, unstable achievers and non-achievers. These results were largely independent of the initial degree of handicap assessed by the TQ upon admission to the hospital. Several important aspects are discussed.

Introduction

In December 1998 all 1348 patients that had been admitted to our hospital for indoor treatment between autumn 1995 and 1997 were asked to complete a battery of self-rating questionnaires, including the German version of the Tinnitus-Questionnaire (TQ), originally developed by Hallam *et al.* (1988).

Eight hundred and thirty patients (62%) participated, 490 of these patients were analysed for the here presented results.

Methods

The TQ measures the level of subjective tinnitus-related stress on six dimensions: Emotional distress (E), Cognitive distress (C), Intrusiveness (I), Auditory perceptual difficulties (A), Sleep disturbances (SI) and Somatic complaints (So). The global score is simply the sum of all scales, ranges from 0 to 84 points and is categorised on four levels of distress from "light" over "moderate" and "severe" to "very severe" tinnitus-related distress.

The TQ is part of the routine diagnostic assessment of the Tinnitus-Clinic Arolsen. It is completed by all patients upon admission to hospital and after treatment, thus enabling evaluation of some important, tinnitus-related aspects of treatment. The TQ score as part of the post-examination was assessed to allow further examination of the course of tinnitus-compensation, the most important ques-

tion being, if the expected treatment success, as defined through the TQ, was stable. The main hypothesis being that there would be an overall reduction of the mean TQ score and there would be no significant increase one to three years later. Furthermore, we were interested in examining the course of tinnitus-compensation in relation to the different levels of subjective tinnitus-distress assessed before treatment.

Results

We analysed complete sets of data (TQ before, directly after and one to three years after treatment) of 490 patients. 62% were female, 38% male; the overall mean age upon admission to the hospital was 51 years (16–78 years of age) with no significant difference between men and women. The average indoor treatment was 6 weeks, ranging from three to twelve weeks; the average tinnitus history upon admission was 5 years, ranging from less than one year to 38 years.

The mean TQ-score before treatment was 46 points. 18% of all patients showed a light, 30% a moderate, 31% a severe and 21% a very severe degree of subjective tinnitus-related distress.

Directly after treatment the mean TQ-score went down to 32 points. The t-test for paired samples proved this to be a highly significant reduction ($p < 0.001$). Further t-tests showed this result to be a reflection of a highly significant reduction of points on each of the six dimensions, thus indicating a clear overall success of treatment. Independent analysis of the TQ-score for the four different levels of subjective tinnitus-related distress assessed upon admission revealed an interesting finding: although significant success of treatment was found

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on all levels, success increased with level of distress. "Very severe" patients scored 20 points less directly after treatment, "severe" patients 15 points, "moderate" patients 13 points, whereas "light" patients merely scored 6 points less. One to three years after treatment the mean TQ-score increased significantly ($p < 0.05$) by three points up to a global score of 35 points. Further analysis showed this increase to be mainly due to an increase of distress on the scales "Intrusiveness" (I) and "Auditory perceptual difficulties" (A), whereas "Emotional distress" (E), "Cognitive distress" (C), "Sleep disturbances" (Sl) and "Somatic complaints" (So) remained stable.

However, compared with the mean TQ-score before treatment, there is still a highly significant decrease (11 points) of the global TQ-score and on all six dimensions, implying a general overall success.

Examination of the course of tinnitus-compensation on a more specific level led to four distinctly different groups.

Stable achievers: a highly significant reduced mean TQ-score directly after treatment that was not significantly different one to two years later.

Late achievers: the mean TQ-score before and directly after treatment did not differ significantly. However, one to two years later the TQ-score had decreased highly significantly.

Unstable achievers: initially a clear treatment success directly after treatment, but, unlike the stable achievers, the mean TQ-score increased highly significantly one to three years later. However, the mean TQ-score stayed significantly lower than before treatment.

Failure: a highly significant increase of the mean TQ-score directly after treatment and again a significant increase one to three years later.

Most patients (69%) belonged to the group of stable achievers, 14% were insatiable achievers, 9% late achievers and 8% belonged to the failure group. These different courses of tinnitus-compensation were found on all levels of subjective tinnitus-related distress, though the initially "light" distressed patients had a higher proportion of failures than any other level (42%), the "very severe" distressed the lowest proportion (8%).

Age, sex, profession, duration of tinnitus, further otological diagnosis and clinically relevant psychological disorders are not adequate variables to predict success or stability of treatment. The only variable we found to be of some relevance was the degree of hearing loss. All patients without relevant hearing loss (maximum hearing loss 10 dB) were stable achievers, whereas an increase of hearing loss increased the possibility of an unstable success or failure. There was no significant relationship between hearing loss and degree of subjective tinnitus-related distress.

Discussion

The results show a clear and relatively stable decrease of the mean TQ-score directly after and one to three years after indoor treatment at the Tinnitus-Clinic Arolsen, regardless of the level of subjective tinnitus-related distress. Thus, we conclude the following:

The TQ is a good measure for assessing the individual level of subjective tinnitus-related distress and to identify different courses of tinnitus-compensation.

The therapy-concept of our hospital allows successful treatment, defined by reduction of tinnitus-related distress, for patients of all levels of distress, though patients with a higher level of distress before treatment generally profit more from treatment than patients with an initially lower level of distress.

Stability of success is independent of the initial TQ-score and its levels of distress as well as of the TQ-score and its levels of distress directly after treatment or one to three years later. A "very severe" patient is likely to gain a lot from indoor treatment, but he will still be in the category of "severe" distress after treatment, which is generally classed as a certain sign of decompensation. However, this patient is just as likely to stabilise his success as an initially "severe" distressed patient who rates himself as "moderate" directly after treatment.

It seems as though the categories "light", "moderate", "severe" and "very severe" say far less about the degree of tinnitus-decompensation and need for treatment than generally assumed in theory and practice. Even more so when taking into account the fact that on all levels of distress most in-patients suffer not only from tinnitus, but also from primary and secondary clinically relevant psychological disorders (72% of the "light", 92% of the "very severe" patients), as we have found in our patients. Further research is obviously necessary. Particularly trying to identify variables that determine whether or not a patient will experience stable success in compensating tinnitus-related distress should be recognised and treated as a question of high importance.

The results presented here are part of an extensive katamnesis-study. Further inquiries are welcome.

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Characteristics of tinnitus and related quality of life in people who attend at tinnitus clinic

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We report here the results of a questionnaire-based study sent to two groups of people. The first group were tinnitus sufferers who had attended and been discharged from the tinnitus clinic, the second group were sufferers still on the waiting list. The design of the questionnaire as well as some of the preliminary results concerning the epidemiological features of tinnitus in this group of sufferers will be discussed in this poster.

Introduction

Tinnitus is a chronic condition for which 2.5% are referred for specialist opinion in the UK (Davis, 1995) [1]. The effect of tinnitus on different aspects of life and health of the sufferers varies greatly, depending on several factors related to tinnitus, and to how people react to it. Understanding the burden of tinnitus will be of vital importance in determining what needs to be done in the treatment and rehabilitation process.

Methods

A questionnaire was developed to include three sections:

- (1) Tinnitus questionnaire, intended for the person reporting tinnitus, including questions about the nature of tinnitus, duration, side, severity, possible handicaps, associated hearing difficulties, use of hearing aids and tinnitus masker/re-training devices.
- (2) The SF-36 Aspects of Health Questionnaire, intended for the person reporting tinnitus, to test for physical and mental health aspects of the individual.
- (3) The Quality of Family Life Questionnaire, intended for the family as a whole and including two sections:
 - (A) The difference in the quality of family life experienced as a direct consequence of attending the tinnitus clinic.
 - (B) How the family feels about the same aspects now.

The questionnaire was sent to 281 families of individuals who have attended and been discharged from the Tinnitus Clinic (Group B), and 101 families of individuals on the waiting list to attend the Tinnitus Clinic, excluding section A from the Quality of Family Life Questionnaire (Group A).

Results

The overall response rate was 71% (89% for Group A and 69% for Group B after three reminders). Both groups were matched for age, sex and mean hearing threshold. Individuals in group A were

Table 1 The difference between Group A and B regarding how tinnitus affects several aspects of the individual's quality of life.

| | Severe | Moderate | Slight | No |
|----------------|--------|----------|--------|-------|
| Annoyance | | | | |
| Group A | 57.6% | 31.8% | 10.6% | 0% |
| Group B | 48.9% | 32.3% | 15.6% | 3.2% |
| Depression | | | | |
| Group A | 20.6% | 20.6% | 28.4% | 30.7% |
| Group B | 14.3% | 20.9% | 15.3% | 49.5% |
| Tension | | | | |
| Group A | 29.5% | 34.1% | 22.7% | 13.6% |
| Group B | 19.9% | 32.1% | 15.8% | 32.1% |
| Insomnia | | | | |
| Group A | 27.3% | 30.7% | 18.2% | 23.9% |
| Group B | 18.9% | 22.4% | 15.3% | 43.4% |
| Anxiety/Future | | | | |
| Group A | 33% | 35.2% | 14.8% | 17% |
| Group B | 16.3% | 30.1% | 17.3% | 35.7% |
| Anxiety/Future | | | | |
| Group A | 15.9% | 33% | 26.1% | 25% |
| Group B | 7.7% | 19.4% | 21.4% | 51.5% |

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generally more severely affected by the tinnitus complaint for aspects regarding the quality of life of the individual.

Another interesting finding was the decreased prevalence of right sided tinnitus in both groups compared to left sided and bilateral tinnitus (27.3% of Group A had right sided tinnitus, compared to 33% left sided, and 36.4% in both ears, while in Group B 18.9% had right sided tinnitus compared to 38.3% left sided and 36.7% in both ears). This trend is in agreement with previous studies. Stouffer and Tyler (1990) [2] found that left sided tinnitus was more prevalent than right sided tinnitus in their study group (40.7% and 34.6% respectively) and Axelsson (1995) [3] found that 22.7% of his female patients suffered from left ear tinnitus compared to 21% right ear tinnitus. In the male population the percentage was 21% left ear tinnitus and 13% right ear tinnitus. Other categories included “both ears”, “both, more to the right”, “both, more to the left” and “in the head”. Our study showed no correlation between left sided tinnitus and severity of tinnitus (as represented by the annoyance measure) in agreement with our previous work (Davis, 1995) [1], but a statistically significant correlation was found between left sided tinnitus and insomnia (PR = 0.0338) and depression (PR = 0.0020) in comparison with right sided tinnitus (Table 2). More studies on a larger sample of the population are recommended to verify this finding and suggest possible explanation for it.

Regarding how the individuals rated their hearing difficulties and their use of hearing aids, we found that 38.8% of the individuals in Group B are using hearing aids, while 77.3% of them said they have some form of hearing difficulty. In Group A, only 17.1% of the study group used hearing aids, while 73.5% reported hearing difficulty (Table 3).

Full results of the SF-36 Aspects of Health Questionnaire and the Quality of Family Life Questionnaire are discussed elsewhere (*Quality of family life of people who report tinnitus*).

Table 2 Comparison between people who complain of right sided/left sided/both ears tinnitus regarding some quality of life measures

| | No | Slight | Moderate/severe |
|-------------------|-------|--------|-----------------|
| Annoyance | | | |
| Both ears/head | 1.1% | 16.2% | 82.7% |
| Rt side | 0% | 13.1% | 86.9% |
| Lt side | 3.9% | 10.7% | 85.4% |
| Tension | | | |
| Both ears/head | 22.1% | 19.2% | 58.7% |
| Rt side | 29.5% | 19.7% | 50.8% |
| Lt side | 19.2% | 17.3% | 63.5% |
| Depression | | | |
| Both ears/head | 46.2% | 13.5% | 40.4% |
| Rt side | 49.2% | 27.9% | 23% |
| Lt side | 29.8% | 23.1% | 47.1% |
| Insomnia | | | |
| Both ears/head | 32.7% | 18.3% | 49% |
| Rt side | 47.5% | 14.8% | 37.7% |
| Lt side | 27.9% | 17.3% | 54.8% |

Table 3 Hearing difficulty and the use of hearing aids in the study group

| | Group A | Group B |
|---------------------------|---------|---------|
| No hearing difficulty | 20.5% | 19.4% |
| Slight hearing difficulty | 43.2% | 30.1% |
| Moderate difficulty | 27.3% | 33.2% |
| Severe difficulty | 6.8% | 10.2% |
| Use hearing aid | 17.1% | 38.8% |
| Don't use hearing aid | 79.6% | 55.1% |

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Treatment history of incoming patients to the Tinnitus & Hyperacusis Centre in Frankfurt/Main

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The history of previous approaches, before patients received Tinnitus Retraining Therapy (TRT) in the Tinnitus & Hyperacusis Centre in Frankfurt/Main provides insight into typical methods used in Germany for tinnitus treatment. A survey sample of 250 (42.52%) was selected randomly from a total of 588 patients treated with TRT in our Centre. The subjects received a questionnaire consisting of 12 questions, including questions about previous treatments, and duration of complaint.

Sixty-six (26.4%) completed responses were received. Typically patients were treated with:

- (1) infusions (Trental or similar),
- (2) hyperbaric chamber,
- (3) general hospitalization,
- (4) health resort,
- (5) putting on sicklist.

Obviously patients coming to us were not helped by the previous treatments. It is important to recognize however, that these approaches could be potentially effective, but were not effective for our patients.

However taking into account the cost factor, and even assuming the same effectiveness of other methods as TRT early implementation of TRT appears to be the economically optimal for the medical insurance system in Germany.

Introduction

During the first interviews with our patients we recognized that practically all had received some kind of treatment for their tinnitus prior to coming to our Centre for TRT. We decided to investigate number and duration of these treatments and developed a questionnaire to be filled out by the patients of our Centre.

Method

From a total of 588 patients of the Centre 250 (42.52%) were randomly selected. The questionnaire consisted of 12 questions, with special attention to questions about previous treatments. The questionnaire was mailed to the patients. 66 (26.4%) completed questionnaires were received. The number of patients in the graphs varies due to the fact, that not all of the 66 patients got all treatments specified.

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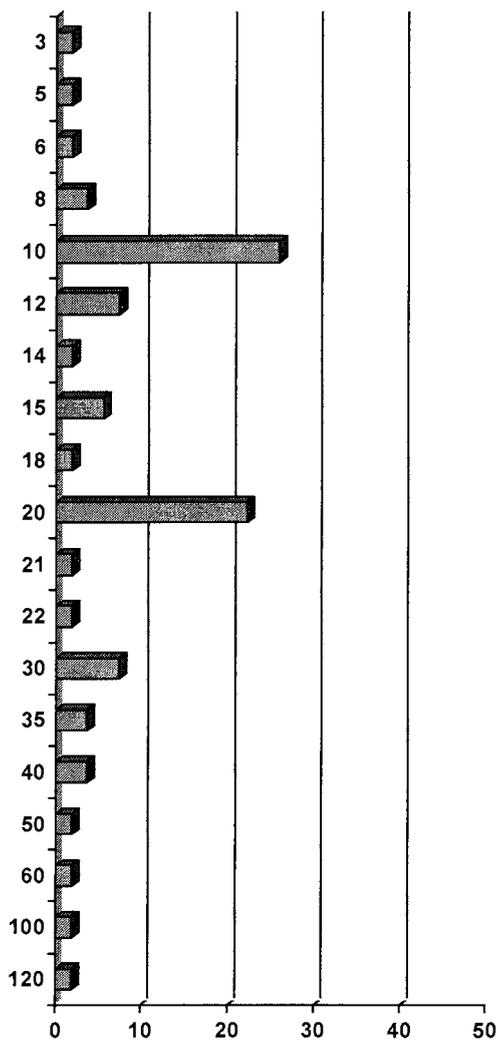


Figure 1 Number of infusions patients received (n = 54)

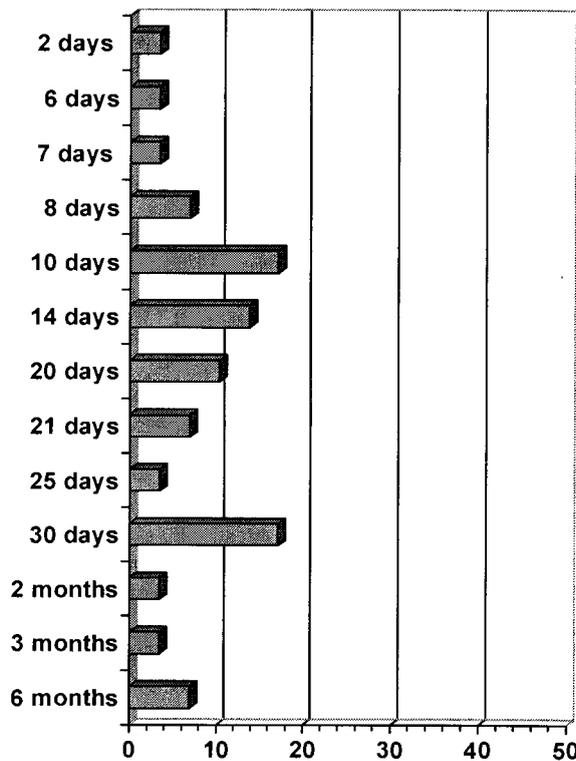


Figure 3 Duration of hospitalization (n = 29)

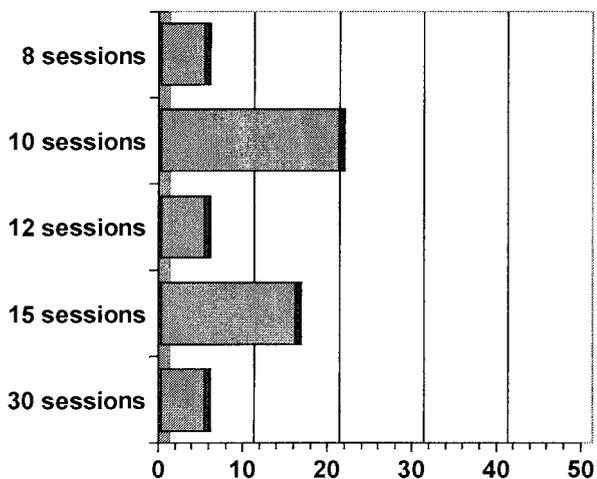


Figure 2 Number of sessions in the hyperbaric chamber (n = 19)

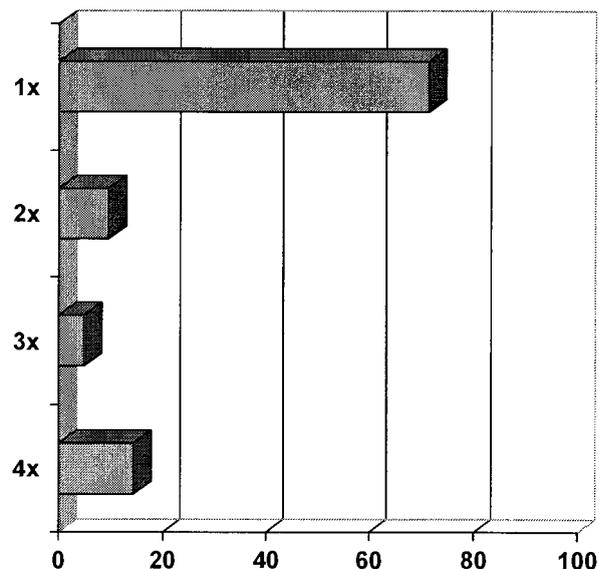


Figure 4 Number of stays in health resorts (n = 21)

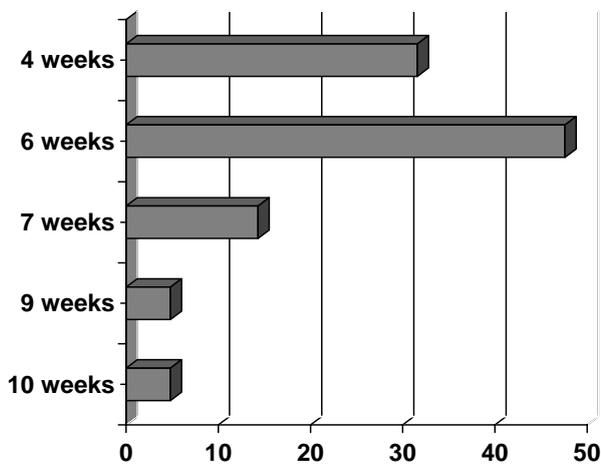


Figure 5 Duration of stays in health resorts (n = 21)

Discussion and conclusion

Patients coming to our Centre were obviously not helped by previous treatments. Most of them reported added strain when they recognized that the treatments did not work for them. In many cases this meant added distress and had a negative effect

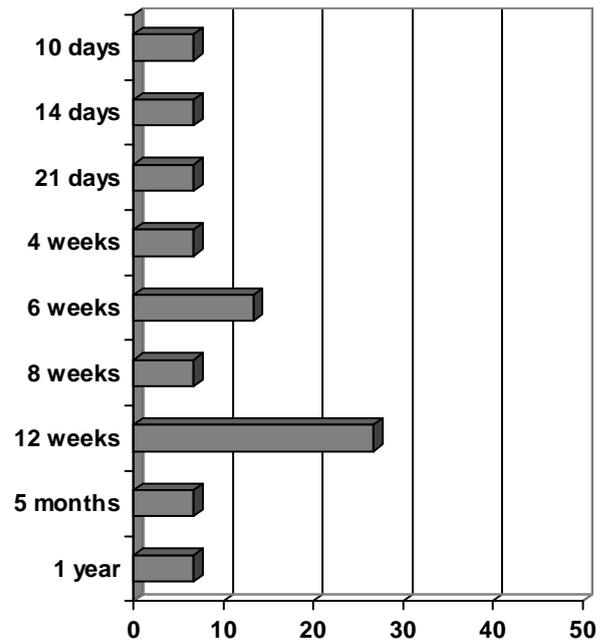


Figure 6 Duration of being on the sick-list (n = 15)

on their tinnitus. It is important however that these approaches can be potentially effective but were not for our patients. Another factor to take into account is the cost of the treatment compared to other methods. Early implementation of TRT appears to be economically optimal for the medical system in Germany.

Tinnitus after acute acoustic trauma

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Acute acoustic trauma (AAT) from firearm shooting is a common cause of tinnitus. The natural history and long-term effects of AAT-induced tinnitus are not well known. We have investigated the duration and long-term annoyance of AAT-induced tinnitus in 418 conscripts who had suffered AAT during their service in the Finnish Defense Forces 11–15 years earlier.

Tinnitus was a prominent symptom immediately after AAT in all cases. In most cases it disappeared or was attenuated to an undisturbing level within a few weeks following trauma so that in more than two thirds of the cases tinnitus was no longer present three months after the AAT. Thirty percent of the patients (122 conscripts) stated that they still had tinnitus when they finished their military service. We have tried to contact this group of patients for a long-term follow-up. In 101 cases (83%) this has been possible. Of these 101 patients 42 claimed that they still suffered considerably from tinnitus (11–15 years after the AAT) and were interested in any new treatment possibility if available.

Introduction

Acute acoustic trauma (AAT) from firearm shooting is a common cause of tinnitus. The natural history and long-term effects of AAT-induced tinnitus are not well known. We have investigated the duration and long-term annoyance of AAT-induced tinnitus in 418 conscripts who had suffered AAT during their service in the Finnish Defense Forces 11–15 years earlier.

Patients and methods

The patient material consists of conscripts who were treated at the ENT-ward of the Central Military Hospital of Helsinki because of AAT during a period of 1.9.83–31.5. 1988. At the first visit all the patients had tinnitus and showed a threshold shift of more than 15 dB at least at one frequency. The causative weapon was in about 85% of the cases hand-held weapons and in 15% large calibre weapons or explosions. The patients were generally treated with normobaric oxygen for 90 minutes twice daily for seven days and followed-up with audiometry testing in average until 70 days post-trauma.

For the long-term follow-up an inquiry was sent to all former patients who had claimed at the last visit still having tinnitus. The individuals with prolonged/persistent tinnitus have then been further examined during a clinical and audiological follow-up visit at the Helsinki Ear Clinic.

Results

All the patients had tinnitus when they visited the ENT-ward for the first time, usually 1–3 days after AAT. Of 418 patients 122 stated at the last visit that they still were suffering from tinnitus.

We were able to get a response to our inquiry in 101 cases (83%). Of these 101 patients 42 still had distressing tinnitus and were interested in any treatment available (Table 1). In 24 cases there was still tinnitus but it was not distressing and in 35 cases tinnitus had disappeared (Table 1).

Table 1 Occurrence of tinnitus 11–15 years after acute acoustic trauma (AAT), n = 101

| | |
|--------------------------|----|
| distressing tinnitus | 42 |
| non-distressing tinnitus | 24 |
| no tinnitus | 35 |

Both a previous hearing impairment (as noted by audiometry screening before entering the military service) and the severity of AAT-induced threshold shift in hearing sensitivity were directly correlated to the persistence of tinnitus (Table 2).

The causative weapon was in about 85% of the cases hand-held weapons and in 15% large calibre weapons or explosions. Independent of the etiological weapon, the frequency of tinnitus was around 6.0 kHz. There were no significant differences in causative weapons or tinnitus frequencies between conscripts with long-standing and short-term tinnitus (Tables 3 and 4).

Table 2 Frequencies of previous hearing impairment (HI) at screening audiometry in different tinnitus groups and severity of TTS/PTS in different tinnitus groups

| | Individuals with prolonged tinnitus n = 122 | Short-term tinnitus n = 296 | |
|-----------------------------------|---|--------------------------------|---------|
| <i>HI at screening</i> | | | |
| normal | 84% | 87% | |
| abnormal | 16% | 13% | |
| <i>Severity of AAT-induced HI</i> | | | |
| | kHz | mean dB | mean dB |
| TTS | 0.5-1-2 | 13 | 14 |
| | 3-4-6-8 | 41 | 30* |
| All frequencies** | | 200 | 162* |
| PTS | 0.5-1-2 | 6 | 5 |
| | 3-4-6-8 | 27 | 12* |
| All frequencies** | | 123 | 61* |

*p < 0.01; ** summa (dB) of frequencies 0.5–8 kHz

Table 3 Causative weapons of AAT

| | With prolonged tinnitus n = 122 | Short-term tinnitus n = 296 |
|---------------|------------------------------------|--------------------------------|
| Hand-held | 82% | 85% |
| Large calibre | 18% | 15% |
| Bazooka | 11% | 6% |
| Cannon | 3% | 6% |
| Explosions | 4% | 3% |

Table 4 Mean tinnitus frequency as measured at the first visit after AAT in relationship to causative weapon, n = 347.

| | kHz |
|-----------------------|-----|
| Hand-held weapons | 6.5 |
| Large calibre weapons | |
| Bazooka | 6.1 |
| Cannon | 5.5 |
| Explosions | 6.4 |

Discussion

This study shows that tinnitus is the major symptom of AAT from firearm-shooting, which however, usually is temporary and disappear within a few days of weeks after AAT. In about one-quarter of cases, however, the duration of tinnitus is prolonged. Of these cases, in about one third tinnitus disappears within one year and in one third tinnitus is reduced to a nondisturbing level. However, about 8% of the patients with AAT from military exercise seem to suffer from distressing tinnitus for the rest of their lives.

Individuals with previous sensorineural hearing loss are more susceptible to get distressing tinnitus from shooting. There is also a direct correlation between the persistence of tinnitus and the severity of hearing impairment induced by AAT. The subjective symptoms of these former conscripts who had suffered AAT during their obligatory military service are often worsened because in many countries tinnitus alone or tinnitus in association with only a high tone hearing loss is not considered to be a handicap worth of any compensation.

Tinnitus awareness in the general public, hearing health specialists and primary care physicians

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The specific aims of this study were to conduct a randomized survey using a telephone interviews for the general public, and printed questionnaires for health care professionals, to: (1) measure the awareness of tinnitus in the general public, hearing care professionals, and primary care physicians; (2) measure the perceived incidence of tinnitus; and (3) to identify likely treatment strategies.

Methods

In the first survey, general public, 409 telephone surveys were conducted by specially trained interviewers with a random sample of US households. Approximately 100 surveys were completed in each of four geographic regions with sample drawn from individual states in proportion to each state's population. Weighting based on the number of completed surveys in each region factored by the actual population in that region was utilized to eliminate regional bias in the total percentages presented.

Results

The results are representative of the US general population with a maximum sampling variability of $\pm 4.85\%$ at the 95% confidence level.

In the general public respondents were asked whether they knew the term tinnitus and if so to provide a definition of it. Over half (53%) of those who said they knew the term tinnitus gave a correct answer. Those who originally admitted they did not know the term tinnitus were asked if they were aware of a health condition with the symptoms of ear ringing or head noises. Of these people, 62% said they had heard of such a condition. Generalizing from these data we can arrive at a measurement of the overall awareness of tinnitus in the US. Sixteen percent of the population is aware of and can correctly define tinnitus. Another 49% are familiar with the symptoms but don't know the name. Overall, one in three respondents (31%) said

they are familiar with the term "tinnitus". Approximately a third of the population don't know the name or the symptoms.

Six percent of the total sample stated that they have the symptoms of tinnitus. Almost 14% have a relative or an acquaintance with the condition. Just over three-quarters of the study sample (79%) have no direct experience with tinnitus.

If the symptoms of tinnitus were experienced, respondents indicated they would seek the help of their doctor (54%) or some type of specialist (45%). Only 10% didn't know what they would do or where they would look for help.

In the second survey of hearing health specialists 1203 surveys were mailed at random to a list provided by a professional list broker. One hundred sixty one valid responses were received for a response rate of 13%. The specialties surveyed were Audiologists, Otologists, and Otolaryngologists/ENT. The names chosen for the mailing were repre-

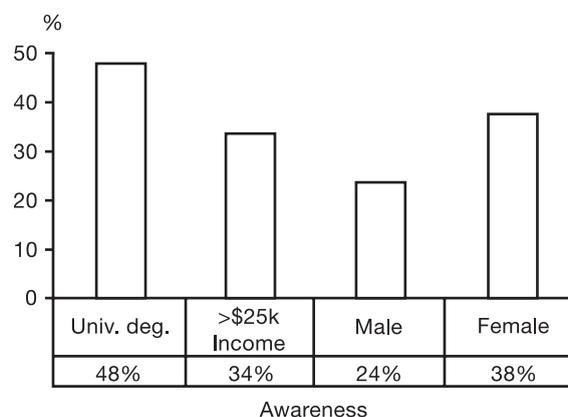


Figure 1 Tinnitus awareness

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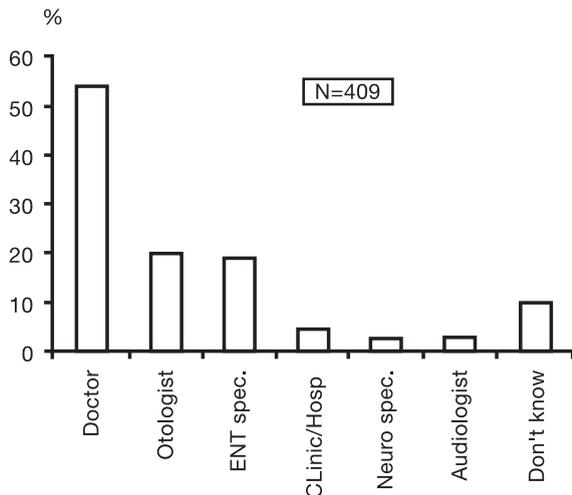


Figure 2 Tinnitus treatment resources

sentative, based on geographic location and specialties of the total names available. One percent of the respondents offered that they have tinnitus (this was not a question). Of this group, 99% were familiar with tinnitus offering a variety of definitions. Treatment for tinnitus was offered by 68% of those surveyed.

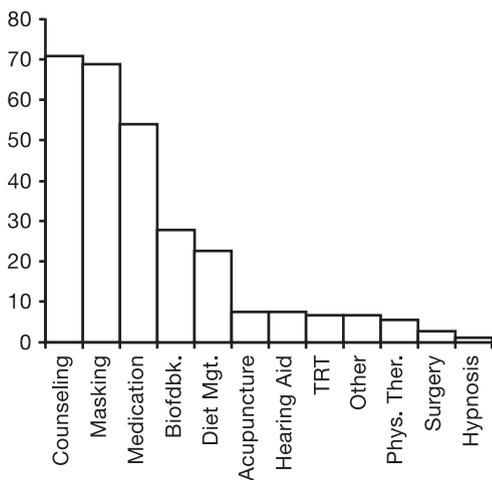


Figure 3 Tinnitus treatments by *Hearing Health Specialists*

Of those who did not offer treatment the most usual reason was that it was not within his or her specialty, or they didn't have the expertise. Of the non-treaters, 40% referred patients elsewhere, most to an otolaryngologist/ENT.

Of this group 62% were aware of the ATA before receiving this survey, and 74% said they would consider using ATA as a resource for tinnitus information.

At the same time 1997 surveys were mailed to a random sampling of Primary Care Providers. The 137 returns provided a response rate of 7%. Five percent of these respondents indicated they had tinnitus (this was not a question). The group was made up of 1431 Internal Medicine Specialists and 566 Family Medicine Specialists. Everyone in this group indicated a familiarity with tinnitus. Fifty-one

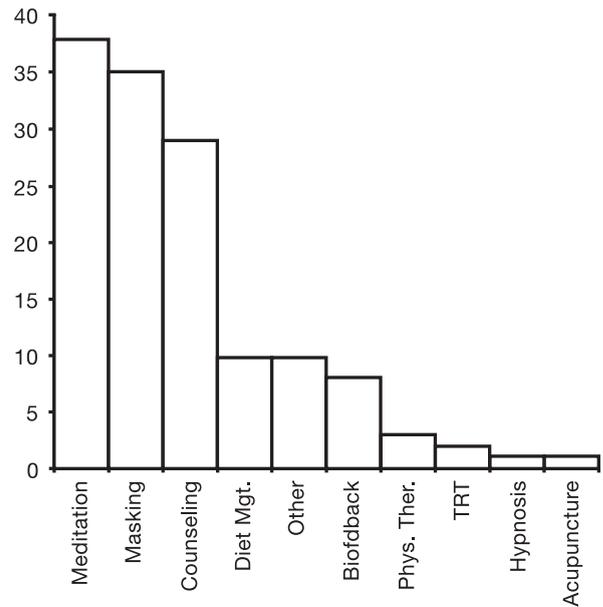


Figure 4 Tinnitus treatments by *Primary Care Physicians*

percent indicated that they provided treatment for tinnitus.

Of those who did not provide treatment the most usual responses were that it was not within their specialty or they did not have the expertise. Of the non-treaters 77% referred patients elsewhere, most often to an Otolaryngologist/ENT. Only 22% of this group knew about the ATA before receiving this survey.

Discussion and conclusion

Tinnitus awareness measurement prior to these studies had been obtained only as a measurement of general understanding and treatment utilization. American Tinnitus Association surveys of 1986, 1992, 1996. In 1986, 83% of the patients responding were told to "Go home and learn to live with it". By 1996 that percentage had decreased to 74%. In 1986 only 31% of the respondents had tried some form of treatment. By 1996 that percentage had increased to 60%. In 1986 respondents rated only 33.7% of physicians or professionals as being helpful. By 1996 that percentage had increased to 58.2%. It appears that as awareness increases not only are doctors perceived as being more helpful, but patients seek and utilize more forms of treatment.

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Epidemiology of tinnitus and hyperacusis in Poland

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Tinnitus is a symptom which affects about 17% of general population all around the world. There has been no epidemiological data on the incidence of tinnitus in Poland so far. The Institute of Physiology and Pathology of Hearing in Warsaw coordinates the programme of epidemiological research in all over the country. The obtained results allow us to determine the incidence of tinnitus and other hearing disorders in adults (17 years and older). A special questionnaire, composed of 13 questions, was elaborated. Twelve thousand sampling at random from the electoral registers of the three regions was performed. The data was collected by personal interview. The results indicate that tinnitus is present in about 20% of our population, constant tinnitus affects approximately 5%, and hyperacusis is perceived by more than 15% of population. The results of Polish epidemiological research confirm high incidence of tinnitus in our country.

Introduction

The prevalence of tinnitus varies with each population that has been studied. Coles [1] reported that about 15% of adults in the United Kingdom appear to have or to have had spontaneous tinnitus lasting over 5 minutes. At least 8% experience tinnitus causing moderate or severe annoyance. The National Health Survey conducted in the United States in 1979 by the Public Health Agency estimated that 36 million American adults (that is about 17% of the population) have tinnitus in some form. Of that number, 7.2 million were identified as having severe form [2]. Chung *et al.* [3] examined the prevalence of tinnitus in a large population of noise-exposed workers and found that only 6.6% of that had tinnitus. Singer *et al.* [4], in a sample of almost 7000 adults reported that only 8.6% of that group experienced tinnitus that occurred more than momentarily. The main factors considered to affect the probability of developing tinnitus have included sex, age, socioeconomic status, hearing loss and noise exposure.

Methods

The special questionnaire composed of 13 simple questions was prepared. First, it was tested on the small sample of nearly 1000 people, living mainly in Warsaw. Then it was changed a little to be more understandable. The questions concerned such factors as sex, age, place of living, occupation, the

presence of tinnitus lasting over 5 minutes, the presence of constant tinnitus, its annoyance (measured on an analog visual scale from 0 to 10), the possible causes of tinnitus, the presence of hyperacusis and other problems with hearing. The data was collected by personal interview in three different regions of Poland: north-eastern, which is predominantly rural, with a rather low socioeconomical status; central, with the capital of Poland – Warsaw, with the highest socioeconomical status, mostly urban and partially agricultural, and southern – Silesia, which is mainly industrial region with the high degree of environmental pollution. The investigated population was divided into 7 age groups.

We analysed data from 10349 respondents (age 17 and over). 52.7% of them were men and 47.3% were women. 31.9% investigated were from the central region of Poland, 31.3% from the north-eastern part of our country and 36.8% lived in the region of Silesia.

Results

Prevalence

Tinnitus lasting more than 5 minutes was reported by 20.1% of the whole population. Constant tinnitus was perceived by 4.8% of respondents.

Age and sex

The prevalence of tinnitus and constant tinnitus increases with age. The highest incidence of tinnitus was found in the group of the oldest people (age over 75) – 52.8%, whereas the youngest group (up to 25 years) has the lowest ratio (9.7%). The pro-

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portion of constant tinnitus in the tinnitus population also increases with age.

There is a small but significant trend for a higher prevalence of tinnitus among males than among females (21.3% and 18.8%, respectively). But the prevalence of constant tinnitus is not related with sex (4.9% of males and 4.8% of females).

Place of living

There is statistically significant difference between the place of living of the respondent and the prevalence of tinnitus. Most often it affects people living in the central part of Poland (the prevalence of tinnitus in this group is 23%). The prevalence of tinnitus in the other parts of Poland is 21.8% at Silesia and only 15.2% in the North-East. But, interestingly, the prevalence of constant tinnitus is highest in the north-western region (5.8%) in comparison to central part (4.7%) and Silesia (4.2%).

Annoyance of tinnitus

For 13.8% people with tinnitus it wasn't a problem at all (annoyance = 0). Mild and moderate annoyance (from 1 to 5) was reported by more than a half of tinnitus population (55%). The severe annoyance (from 8 to 10) was a problem for 9.7% of them. The annoyance of tinnitus is not related to sex, but is related to age of the respondents. Increasing age is accompanied by an increasing incidence of severe, disabling tinnitus.

27.1% of people with tinnitus and 49.2% with constant tinnitus are seeking professional help. That is, 5.4% of Polish population are tinnitus patients.

Possible causes of tinnitus

The most frequent cause of their tinnitus, according to the respondents, was noise. Tinnitus after exposure to noise was reported by 10.3% of respondents. It was occupational noise, acute noise (explosion, shooting) and listening to amplified music. Other main possible causes were: weather (6.3%), hearing loss (4.6%), infections (4.3%), stress (2.4%), head trauma (1%) and ototoxic drug exposure (0.5%). 3% of the respondents are not aware of the cause of their tinnitus and don't see any correlation of this symptom with anything.

Hyperacusis

This symptom was present in 15.2% cases. Hyperacusis was reported by 12.5% of investigated women and 17.6% of investigated men and this difference is statistically significant. Hyperacusis most commonly occurs in the central part of Poland, where almost one fourth (24.9%) of adults reported it. In the region of Silesia the prevalence of hyperacusis is 12.2% and in the North-East it's only observed by 8.9% of people. The differences among these regions are highly significant. Almost

40% of the tinnitus population in Poland reported hyperacusis.

Discussion and conclusions

The prevalence of tinnitus in Poland is higher to those reported by other authors [1,2,3,4]. Maybe it is due to lower socioeconomic status of people living in Poland in comparison with people living in the United Kingdom and USA. Coles suggested that tinnitus prevalence was increased in unskilled patients of lower socioeconomic status compared to professionally employed patients of higher socioeconomic status. But contrary to this is predominance of tinnitus in the central part of Poland with the highest socioeconomic status. The prevalence of tinnitus in Poland is increasing with age, which is similar in other countries [1,2]. An interesting finding is the higher rate of tinnitus prevalence in males, which is not consistent with other authors [1,3]. But it seems reasonable as men are more susceptible to various diseases than women. For that difference may also account greater noise exposure in men. Also the lowest prevalence of tinnitus and hyperacusis in the rural North-East of Poland is what we expected. People living in this region are less exposed to noise, stress and environmental pollution than those living in more industrial, urbanized, polluted parts of Poland. It is difficult to explain, however, why north-eastern inhabitants have more often constant tinnitus than people in more polluted parts of Poland. The results of our survey is consistent with recent German epidemiological research, conducted by Deutsche Tinnitus Liga, where also significant differences of prevalence of tinnitus among various parts of Germany were found [5]. The severity of tinnitus in our country is related to age. According to Hazell [6] this is because the severity of tinnitus is related to the degree of hearing loss.

Our data suggest that the symptom of tinnitus in Poland is frequent and in majority of people is accepted as a "normal" phenomenon or as an occasional minor disturbance. In a distinct group of patients, however, it is severely disabling. It equals over 1 million of Polish people being so affected. We should offer them effective and professional help.

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Epidemiology of tinnitus in Lublin District

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Epidemiological tinnitus research carried on in the 1980s in the USA and Great Britain proved the existence of tinnitus in about 35–45% of adults. About 15% of the subjects were conscious of tinnitus for longer than 5 minutes, while 8% of the examined found tinnitus as a hindrance to falling asleep and having a rest. A very intense tinnitus was observed in 0.5% of the patients [3,4,5]. It means that in Great Britain about 200,000 people suffer from a severe tinnitus [4]. Its occurrence rises in frequency with age, particularly over 40 in women and over 50 in men. A very important factor increasing the prevalence of tinnitus is exposure to noise [4,5].

The aim of the paper was to estimate tinnitus in the Lublin region population depending on age, gender, exposure to noise, and the state of hearing.

Material and methods

Tinnitus epidemiology research was carried out by way of a questionnaire sent to 35,000 adult inhabitants of the Lublin region chosen at random from electoral lists. The number of filled out and received questionnaires was 16,614 (47.5%). The group included 9112 (54.8%) women and 7502 (45.2%) men.

Results and discussion

Tinnitus was reported by 8484 (51.1%) of the inquired. This number included 6270 (37.7%) cases of occasional tinnitus, 2214 (13.3%) of frequent tinnitus, and 275 (1.6%) of the inquired did not answer questions concerning tinnitus. Within the group of women there were more reports concerning tinnitus (53.5%) than in the group of men (48.2%) (Table 1).

Tinnitus lasting longer than 5 minutes was reported in 3246 (19.5%) questionnaires, a little more often by men (19.8%) than by women

(19.3%). There were 5016 (30.2%) of those who experienced tinnitus equally in both ears, 1692 (10.2%) of the inquired reported it more on the right side, and 1687 (10.1%) people heard it more on the left side. In addition, 914 (5.5%) of the questionnaires reported a very severe tinnitus, while 3856 (23.2%) found it moderately disturbing, and 3657 (22.0%) of the inquired did not report any disturbance.

Hearing loss was found in 24.1% cases of tinnitus and these were more frequent in men (27.3%) than in women (21.7%). There were 40.7% of people affected by tinnitus who worked in noisy conditions, with more frequent cases of men (57.3%) than women (28.3%). Figure 1 presents tinnitus incidence lasting longer than 5 minutes depending on the age of the inquired. A clear increase in tinnitus frequency reports is quite evident with age. This increase refers to frequent tinnitus occurrence too, while cases of rarely occurring tinnitus were reported even more frequently by younger people than elders. Out of all those who experienced tinnitus only 23.1% sought the doctor's advice because of this trouble.

Table 1 Reporting tinnitus depending on gender

| Gender | No | | Rarely | | Frequently | | Totally | |
|---------|------|------|--------|------|------------|------|---------|-------|
| | n | % | n | % | n | % | N | % |
| Women | 4093 | 45.7 | 3582 | 40.0 | 1289 | 14.4 | 8964 | 100.0 |
| Men | 3762 | 51.0 | 2688 | 36.4 | 925 | 12.5 | 7375 | 100.0 |
| Totally | 7855 | 48.1 | 6270 | 38.4 | 2214 | 13.6 | 16339 | 100.0 |

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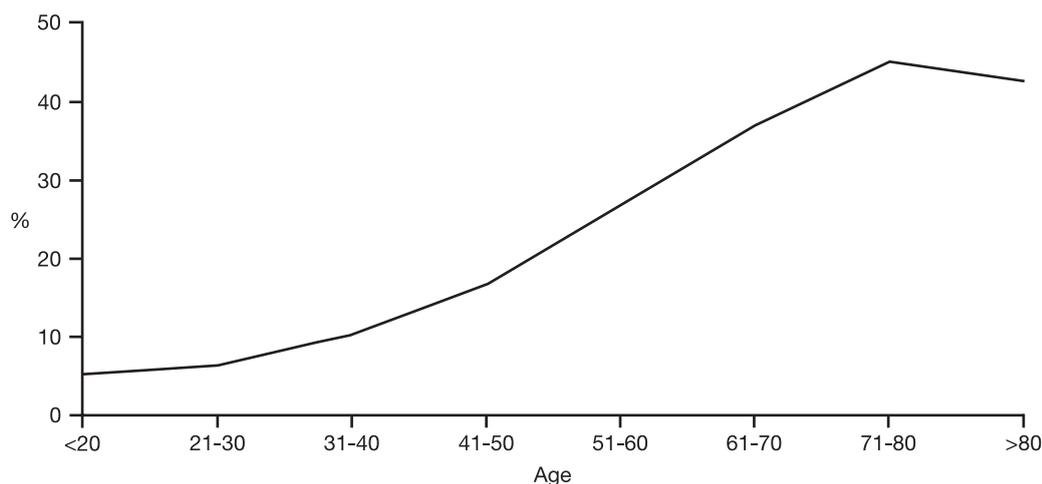


Figure 1 Reporting tinnitus lasting longer than 5 min depending on age.

The questionnaire study indicates a more frequent (51%) tinnitus occurrence in the inquired population of the Lublin region than other authors report [1,2,3,4]. Hazell points out that in Great Britain tinnitus occurred in 35–45% of cases. Those lasting longer than 5 minutes occurred in 17% of the inquired. In the Lublin group tinnitus episodes longer than 5 minutes were reported by 19.5% of the inquired. A large percentage (37.7% of the group) of the experienced tinnitus was described as “rarely occurring”, which implies its small persistence. Cases described as “frequently occurring” were reported by 13.3% of the inquired, similarly to 14.2% in Axelsson’s research [1]. Worth considering is the percentage of tinnitus (5.5%) described as “very severe”, in comparison with 0.5% in the British population [4]. With regard to the Swedish population this percentage was 2.4 [1]. As in the research of other authors, the answers obtained in questionnaires indicate dependence of tinnitus occurrence on age: with older people tinnitus occurs more frequently. Also, the noise factor seems to influence the occurrence of tinnitus; 40.7% of people affected by tinnitus admitted working in noisy conditions, while in the whole group of the inquired this percentage was lower and was 33.5. On the other hand, men reported working in noisy conditions twice more often than women but tinnitus occurred more often in women than in men.

Conclusions

- (1) Questionnaire studies in Lublin region showed that 51.1% inhabitants reported tinnitus.
- (2) Cases of tinnitus lasting longer than 5 minutes are reported by 19.5% of the inquired, while 5.5% of them admit very severe tinnitus disturbance.
- (3) Incidence of tinnitus increases with age.

Summary

Epidemiology of tinnitus was assessed out by means of questionnaires sent out to adult inhabitants of the Lublin District. 16,614 filled up forms were received. The group of inquired people consisted of 9112 (54.8%) women and 7502 (45.2%) men.

Tinnitus was reported by 8484 (51.1%) of the inquired including 6270 (37.7%) persons in whom it occurred rarely and 2214 (13.3%) with frequent tinnitus. 275 (1.6%) of the inquired did not answer the question concerning tinnitus.

In 3246 (19.5%) persons inquired tinnitus lasted longer than 5 minutes. Tinnitus felt equally in both ears was reported by 5016 (30.2%) people, while 1692 (10.2%) persons placed it more on the right side and 1687 (10.1%) of the inquired heard it more on the left side. 914 (5.5%) people found tinnitus very disturbing, 3856 (23.2%) described it as moderately disturbing, and 3657 (22.0%) persons did not report any disturbance.

Acknowledgement: This research was supported by Foundation of Polish-Germany Co-operation.

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Effects of various surgical approaches on Tinnitus

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Surgery may not be considered when the primary symptom is tinnitus. However, it has been reported that the tinnitus control was remarkable in cases controlled their accompanying symptoms by surgery (Fisch, 1974; Kim *et al*, 1995; Shulman, 1997). Predictors and selection criteria for surgery have not yet been established. Purposes of this study are (1) to evaluate the effect of various surgical approaches (cochlear implantation, vestibular neurectomy, chemical labyrinthectomy, etc) on tinnitus and (2) to assess the predictors of outcomes. Fifty-two patients were included for this study as follows; 20 cochlear implantees, 21 chemical labyrinthectomized patients, 9 vestibular neurectomized patients, each 1 cochlear neurectomized and microvascular decompression cases, respectively. Various results were obtained as shown in table 1 and there was no effect of cochlear neurectomy and microvascular surgery on tinnitus.

In conclusion, the cochlear implantation and vestibular neurectomy are very helpful for the tinnitus control and the cumulative data are needed to establish the predictors.

Table 1. Effect of various surgeries on tinnitus control

| | Cochlear Implant N = 27 | Chemical labyrinthectomy N = 40 | Vestibular neurectomy N = 9 |
|-----------------|-------------------------------|---------------------------------------|-----------------------------------|
| Complete relief | 38% | 25%78% | |
| Partial relief | 48% | 23% | 11% |
| Unchanged | 22% | 52% | 11% |
| Aggravated | 0% | 0% | 0% |

Influence of acupuncture treatment on tinnitus in patients with signs and symptoms of temporomandibular disorders: A placebo-controlled study

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The aim of this study was to investigate the effect of acupuncture treatment on tinnitus and temporomandibular disorders (TMD) in tinnitus patients with signs and symptoms of TMD in comparison to a placebo therapy. Sixteen tinnitus patients were first subjected to five placebo treatments using an inactive low level laser and thereafter five acupuncture treatments.

The patients were evaluated by questionnaires and visual analogue scales – VAS for assessment of tinnitus and jaw muscle tension and by clinical stomatognathic routine examination for signs of TMD. Twenty five percent of the patients reported a decrease of tinnitus intensity after placebo compared to 44% after acupuncture treatment. The reduction of tinnitus intensity (VAS) was statistically significant following acupuncture treatment ($p < 0.01$) but not following placebo treatment. At the 6 month follow-up a decrease of tinnitus was reported by 19% of all patients. This decrease was not statistically significant.

It may be concluded that acupuncture in comparison to placebo seems to reduce tinnitus in tinnitus patients with signs and symptoms of TMD in a short term perspective. Further studies are necessary to confirm these findings and to determine strategies for obtaining a long term efficacy using this form of therapy.

Introduction

Tinnitus is defined as the perception of sound in the absence of any appropriate external stimulus [1]. Approximately 15% of the general population report recurrent tinnitus. About 2% are severely disturbed by their tinnitus [2].

Temporomandibular disorders is a collective term for a number of clinical problems that involve the masticatory muscles, the temporomandibular joint (TMJ) and associated structures, or both [3]. Tinnitus is one of the otological symptoms frequently reported by patients with TMD [4] and vice versa higher prevalences of TMD have been found in tinnitus patients than shown in epidemiological studies [5]. The general conclusion from these studies is that there is a relationship between TMD and tinnitus, vertigo, and otalgia but the mechanisms behind this association are, in spite of a number of theories, still largely unknown [6,7].

In a number of studies on TMD and tinnitus the

authors stress the fact that different types of stomatognathic treatment does not only have a good effect on TMD but also on tinnitus [6,7,8,9]. Acupuncture is one of the therapies successfully used in treatment of TMD, especially on symptoms such as jaw muscle pain and tension type headache [10,11].

The aim of this study was to investigate the effect of acupuncture treatment on TMD and tinnitus in tinnitus patients with signs and symptoms of TMD in comparison to a placebo therapy.

Material and Methods

Sixteen patients were selected for this study among tinnitus patients referred to the Department of Stomatognathic Physiology for treatment of signs and symptoms of TMD from the ENT clinic Sahlgrenska University Hospital, Goteborg, Sweden. Nine were male and seven female patients: mean age 46, range from 28 to 63 years. The duration of their tinnitus experience ranged from 6 months to 22 years. Inclusion criteria were: (1) fluctuating tinnitus, (2) normal hearing (HT < 20 dB; 0.5–8 kHz), (3) diurnal bruxism, (4) feeling of fatigue and stiffness in jaw muscles, (5) no previous acupuncture

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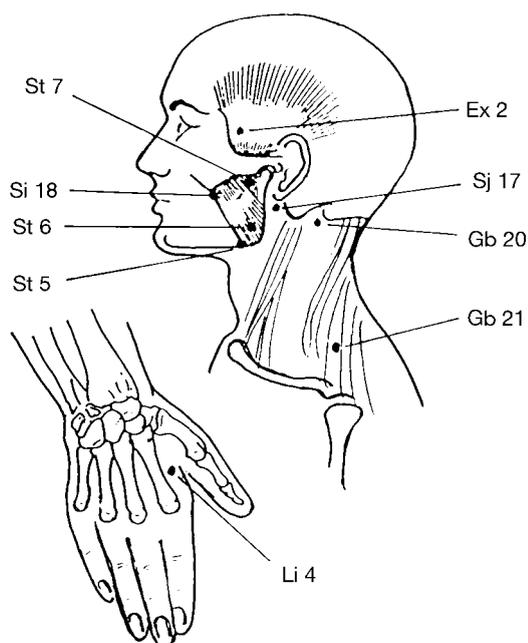


Figure 1 The acupuncture points used in this study

treatment. Erlandsson, Rubinstein and Carlsson 1991 [12] mention fluctuation of tinnitus intensity, normal hearing, diurnal bruxism, jaw fatigue amongst predictors for positive stomatognathic treatment outcome in patients with both tinnitus and TMD.

Placebo and acupuncture treatments were given in acupuncture points Ex2, St5, St6, St7, Si18, Gb20, Gb21, Sj17 and Li4 bilaterally as for treatment of myofascial pain, tension in jaw muscles, and TMD [10,11], Figure 1.

The patients were first subjected to five weekly placebo treatments using an inactive low level laser. After a wash out period of one week, five weekly acupuncture treatments (manual stimulation, 30 minutes each time) were given. The patients were evaluated before treatment, one week after the first treatment period, and one week after the second treatment period by questionnaires and VAS for daily assessment of tinnitus and jaw muscle tension and by a clinical stomatognathic routine examination. Six months after treatment a final evaluation was made by questionnaires.

Standard clinical examination of the stomatognathic system with determination of the Helkimo Clinical Dysfunction Score (CDS) [13] was performed before and after both placebo and acupuncture treatments. All clinical examinations were made by one and the same investigator, who had no knowledge of the therapy given.

Standard non-parametric methods were used to analyse the results.

The study was approved by the local Ethical Committee at the Goteborg University.

Results

Twenty five percent of the patients reported a

decrease of tinnitus intensity after placebo compared to 44% after acupuncture treatment. The reduction of tinnitus intensity (VAS) was statistically significant following acupuncture treatment ($p < 0.01$), but not following placebo treatment. At the 6 month follow-up a decrease of tinnitus was reported by 19% of all patients. This decrease was not statistically significant.

In four patients the tinnitus decrease was parallel to a decrease of jaw muscle tension and CDS. These four patients also reported that their tinnitus was influenced by excessive tooth clenching and/or jaw movements. No significant reduction of muscle tension or CDS could however be shown for the patient group as whole.

Of 9 patients, who reported frequent headaches before the start of the study only three reported headaches at the 6 month evaluation.

Discussion and conclusions

According to a recent search in the Medline database only 16 studies evaluating acupuncture in treatment of tinnitus have been performed during last 20 years. The results are more or less encouraging. Vilholm, Moller and Jorgensen (1998) discuss the results and designs of seven of these studies including their own and conclude that treatment of tinnitus with traditional Chinese acupuncture is not sufficiently effective in a long term perspective and therefore should not be generally recommended for treatment of tinnitus [14].

Our reasons for performing this study were built on: (1) the findings in earlier studies [6,8] and our clinical observations that stomatognathic treatment has a significant effect on tinnitus in some patients with coexisting TMD and tinnitus. (2) the proven effect of acupuncture in treatment of facial muscular pain comparable to other stomatognathic treatments [10,11]. (3) the findings that tinnitus can be altered by jaw movements and maximum voluntary tooth clenching in approximately one third of all patients with tinnitus and TMD [6,8]. Diurnal tooth clenching was found to be the most powerful predictor for successful outcome of TMD therapy in tinnitus patients [8].

The results of this pilot study indicate that acupuncture in comparison to placebo seems to reduce tinnitus and jaw muscle tension in tinnitus patients with signs and symptoms of TMD in a short term perspective. Further studies with larger number of patients and larger number of treatments are necessary to confirm these findings and to determine strategies for obtaining a long term efficacy using this form of therapy. Questionnaires and clinical tests [8] for identification of patients who can benefit of stomatognathic treatment for their tinnitus should be used in selecting of patients for such a study.

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Deep brain stimulation – a new treatment for tinnitus?

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Intractable tinnitus may lead to serious consequences. Study evidence suggests that the central nervous system is involved in generation and maintenance of chronic tinnitus and that tinnitus and other neurologic symptoms such as chronic pain may share similar mechanisms. Brain ablation and stimulation are used to treat chronic pain with success. Recent studies showed that ablation and stimulation in non-auditory areas resulted in tinnitus improvement. This report presents deep brain stimulation (DBS) as a possible alternative treatment for intractable tinnitus.

Introduction

Thirteen to 18.6% of the population has tinnitus [1,2]. The incidence is higher in people with hearing disorders [3,4]. Acoustic therapy, counseling and certain medications provide some relief for most tinnitus patients, but often fail for patients with severe tinnitus. Suicide has been reported in patients with severe tinnitus [5].

Acoustic therapy uses external sounds and remains the mainstay of tinnitus management [6]. Contemporary acoustic therapy also includes intensive psychological intervention, aiming at long-term relief through habituation [7]. Although widely practiced, acoustic therapy remains ineffective in as many as 20% of patients with severe tinnitus [7].

Lidocaine reduces tinnitus perception, but its administration and side effects limit its clinical utility [8]. Alprazolam was shown to reduce tinnitus loudness and help patients sleep [9]. Nortriptyline helps tinnitus patients cope with tinnitus-related mood problems, reduces tinnitus loudness and may improve patients' overall life quality [10].

Effects of other reported tinnitus treatments are not conclusive, although some are used as adjuncts to acoustic and pharmacological therapies.

Tinnitus mechanisms

Tinnitus mechanisms involve both peripheral and central auditory systems. Damage to the cochlea causes hearing loss and often initiates tinnitus, but

the central nervous system (CNS) plays a key part in chronic tinnitus.

Acoustic signals are processed as patterns along the central auditory pathways [11], and certain patterns represent "silence" [12]. Non-auditory systems participate in assessing the meaning of sound [12,13], producing emotional and autonomic responses. Random spontaneous discharges normally exist along the auditory pathway in silence [11]. Such activity provides inhibition for higher level structures, necessary in maintaining normal excitability. Damage to peripheral auditory organs produces abnormally synchronized discharges in the auditory nerve, which, in contrast to the normal random spontaneous activity, is believed to cause phantom auditory sensation [11]. Loss of spontaneous discharges also reduces normal inhibition, causing excitatory/inhibitory imbalance and altered excitability and discharge patterns in auditory nuclei, producing disrupted and false sensations of sound, resulting in distortions and tinnitus.

Jastreboff proposed multi-stage processing by the CNS in chronic tinnitus, including detection, perception and evaluation of tinnitus patterns [13]. A variety of central activities involving auditory and non-auditory systems take place in tinnitus, which enhance the detection process and induce non-auditory responses. The tinnitus signal may be weak, but the neural activity around it causes systemic responses stronger than a louder external sound [12]. Interaction between different neural centers may form oscillatory or reverberant patterns that can sustain on their own and produce lasting tinnitus [14]. The "code of silence" is thus replaced by the tinnitus "code".

Perception of abnormal activity within the auditory pathways is different from that evoked by external sound [13]. Direct electrical stimulation of auditory structures induces perceptions that

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resemble tinnitus, rather than external sound [15]. In animal and human studies, a component near 200 Hz in the spectra of ensemble spontaneous activity is often present when factors known to cause tinnitus are introduced. This component can be eliminated by lidocaine [16]. These evidences suggest that alteration of neuroelectrical activity in the CNS is important in tinnitus generation. Correction of the abnormal activities will change tinnitus behavior and result in tinnitus relief.

A new dimension of tinnitus therapy?

More effective treatments are needed for intractable tinnitus. A review of management tools for symptoms similar to tinnitus may help identify new tinnitus treatments.

Abnormal neuronal interactions in chronic pain and movement disorders

Extensive and complicated connections and feedback loops exist in somatosensory pathways. Central activity is constantly modulated by peripheral input. Loss of peripheral input causes changes in central activity, such as increased discharge rates of neurons in thalamic nuclei. Altered central neural activity patterns are seen following a prolonged course of chronic pain, including memory-like, reverberating activities that can be interrupted by electrical stimulation [17].

Normal motor functions are maintained by balanced inhibitory and excitatory activities among nuclei in the basal ganglia and other related structures. Failure of the sophisticated and delicate balance results in movement disorders [18].

Ablation and stimulation in the thalamus have been used for chronic pain and movement disorders. As imaging and stereotactic guiding technologies improve, the procedures continue to gain wider acceptance with increasingly satisfactory results.

Analogies between mechanisms of tinnitus and chronic pain

Similarities between tinnitus and chronic pain include: (1) They are subjective sensations, (2) Sectioning of afferent nerves is not consistently helpful in either case, (3) The CNS is involved in their generation and maintenance, (4) Peripheral stimulation, electrical for pain and acoustic for tinnitus, provides relief for some patients, and (5) Hyperactivity or hypersensitivity of certain neuronal centers are important mechanisms for tinnitus and pain. It is feasible that new tinnitus treatments might develop from experiences with management of chronic pain [19].

Assuming that mechanisms involved in chronic pain are related to that of tinnitus, it follows that similar treatment principles can be applied in tinnitus. Auditory sensation has been reported during DBS procedures for movement disorders [20], indicating that DBS can modify auditory function.

Deep brain stimulation for tinnitus?

Jeanmonod *et al.* reported improvement in 3 of 6 tinnitus patients treated with ablation in the medial thalamus [21]. In his study, which included neurogenic pain, movement disorders, epilepsy and tinnitus, 45% of the 2012 medial thalamic single units investigated showed low-threshold calcium spike bursts activity. He proposed that a self-perpetuating thalamic cell membrane hyperpolarization was the common mechanism for these neurologic symptoms.

Electrical stimulation of peripheral auditory organs produces tinnitus relief in some patients. Tinnitus relief has also been reported in patients who have received cochlear prostheses or brainstem implants [3,22]. Such relief probably comes from altered activity patterns in auditory pathways by electrical stimulation. Stimulation of more central auditory structures may also provide tinnitus relief through breaking the proposed reverberating patterns responsible for chronic tinnitus [14].

In a preliminary study by the authors [23], 3 of the 7 patients with tinnitus who received DBS treatment for movement disorders reported tinnitus reduction by DBS. The effectiveness is similar to ablation reported by Jeanmonod *et al.* (3 of 6 vs. 3 of 7). It is interesting that ablation and stimulation of non-auditory structures modified tinnitus perception. This implies that tinnitus perception can be mediated by non-auditory as well as auditory structures and that the success of DBS for tinnitus relief is not strictly limited to targeting auditory structures, although auditory structures would seem to be the targets of choice for most effective stimulation.

Summary

Severe tinnitus often does not respond to currently available treatments. Evidence suggests that the CNS is involved in chronic tinnitus and tinnitus may share similar mechanisms with chronic pain. Brain ablation and stimulation provide relief in chronic pain and movement disorders. DBS was also shown to reduce tinnitus perception in a small number of patients. It is thus worthwhile to study DBS for its potential as tinnitus treatment.

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Efficacy of audiological intervention for tinnitus sufferers at the CHUM : Follow-up study

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A retrospective analysis of 77 audiological records was performed to determine the success rate of treatment received. Twelve subjects participated in a focus-group to discuss specific questions on coping with tinnitus. Results suggested that patients sought a wide range of therapeutic approaches and that behavioural and instrumental methods of treatment were the most effective. Also, there is a need to establish within an on site multidisciplinary group environment a follow-up protocol based on patient feedback.

Introduction

In July 1996 and 1999, the Audiology Clinic at Notre-Dame Hospital in Montreal studied the efficacy (patient-wise) of treatment received by tinnitus patients during 1990–1991 and 1995–1996. This project was undertaken to identify the most effective therapeutic approach in view of the type of audiological intervention in use at the CHUM which is highly individualized and tailored to the patients' needs.

Methods

Data analysis indicated that 316 patients were referred to the clinic diagnosed with a variety of hearing problems including tinnitus or with tinnitus only and that 134 patients suffering from tinnitus were referred for therapeutic assistance. Fifty-seven were excluded from this study for a variety of reasons such as patients refused treatment or did not need to pursue treatment, patients could not be traced, etc.

Audiologists analyzed the 77 patient files to collect data relative to the different therapeutic approaches used and satisfaction expressed by the patient on a questionnaire or during the interview at the time of consultation. As recorded in any open-study, the success rate was defined as a patient's ability to reduce discomfort caused by tinnitus [1].

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According to the data, 38 patients (30 to 72 years of age and having tinnitus from 6 months to 20 years) were sent a revised questionnaire and invited to meet as a focus-group to discuss specific treatments and their rate of success. Twelve patients agreed to participate in the group meeting and were asked to prepare a response to the following:

Question 1. If you met someone recently diagnosed with tinnitus and having difficulty to cope, what would be the one advice you would give this individual to help deal with this disability?

Question 2. From all that you have tried, including professional counselling to the advice from a friend, describe the three methods that worked best for you.

Results

The first phase of this study was to analyze the 77 patient files. Results are summarized in Tables 1 and 2.

Table 1 Follow-up results of patients requiring further investigation (N = 49)

| Type of investigation | Positive | Negative | Unknown findings |
|-----------------------------------|----------|----------|------------------|
| Family medicine speciality | | | |
| Dentistry | 3 | 4 | 12 |
| Internal medicine | 4 | 8 | 18 |
| Immunology | | | 3 |
| Neurology | | 3 | 1 |
| ENT | | 8 | 3 |
| Sleep clinic | | | 16 |
| | | | 2 |

Table 2 Effectiveness of different therapeutic approaches

| Type of Approach | Successful | Unsuccessful | Unknown |
|--------------------------------|------------|--------------|---------|
| Medical (N = 35) | | | |
| Dentistry | 1 | 6 | 4 |
| Follow-up sleep clinic | | | 1 |
| Medical investigation | 2 | | |
| Medication | 12 | 6 | 7 |
| Physical medicine * | 4 | 2 | 1 |
| Psychiatry | 1 | | 4 |
| Eustachian tube rehab. | 1 | | |
| Instrumental (N = 35) | | | |
| Electrical stimulation | 2 | | 1 |
| Earplugs | 2 | 4 | 10 |
| Hearing aids | | 1 | 1 |
| Hand-made cancellation device | 20 | 3 | 4 |
| Acoustic devices | | 1 | 2 |
| Tinnitus maskers | | | |
| Alternative (N = 45) | | | |
| Acupuncture | 10 | 12 | 6 |
| Chiropractic | | 5 | 12 |
| Holistic | 1 | | 3 |
| Homeopathy | 1 | 2 | 2 |
| Hypnotherapy | 4 | 1 | 1 |
| Massotherapy | 3 | | 2 |
| Osteopathy | 3 | 2 | 1 |
| Others (vitamins, herbs . . .) | 3 | 4 | |
| Behavioural (N = 62) | | | |
| Counselling and group | | | |
| Dynamics | 4 | 4 | 31 |
| Diversion | 25 | | 3 |
| Environmental changes | 4 | 1 | 1 |
| Nutrition | 4 | 2 | 9 |
| Psychological treatment | 12 | | 8 |
| Sleep control | 5 | | 9 |
| Stress reduction | 27 | 11 | 29 |

*Infiltration, physiotherapy, kinesiotherapy

The second phase of this project was to describe responses from patients who took part in the focus-group. On the one hand, patients indicated that an individual suffering from tinnitus should first seek indepth professional assessment then find resources to better understand and cope with this disability and, finally, identify one's own method(s) of adaptation. On the other hand, discussions within the focus-group indicated patients' concerns regarding developments and improvement in services offered to tinnitus sufferers such as patients need to be informed regularly on scientific information available regarding tinnitus: a need for government intervention to increase public awareness; support groups, although helpful, were depressing for a few individuals; some patients feel discouraged with their limited progress despite following various forms of treatment.

Discussion and Conclusion

Three important conclusions can be drawn from this study:

1. Patients do take advantage, on a trial basis, of the many diversified approaches that are recom-

mended to relieve their tinnitus. Therefore, audiologists must guide patients through the different methods of treatment available and do so in a structured manner.

2. Therapeutic success does vary considerably. There are two groups of approaches which most patients reportedly tried and were found to be more helpful on a long term basis: the behavioural approach directed predominantly towards stress reduction and diversion as well as the instrumental approach which relies on acoustic devices.

3. A significant number of unknown results were noted. This is due mainly to the fact that we rely on voluntary patient feedback and because patients are referred outside the hospital to other public or private resources with whom no specific agreement to provide feedback exists.

In summary, we believe it is the audiologist's responsibility: to guide patients towards finding relief tailored to their needs; to realize that patient feedback is crucial; to recognize that the audiological scientific community benefits from patients' experiences and must depend upon it.

Tinnitus sufferers must be offered a full range of therapeutic approaches by a multidisciplinary team working on site in a mutually cooperative (patient-centered [2,3]) setting which relies on a

strict follow-up protocol based on patient feedback. This centralized method of treatment will be offered at Notre-Dame Hospital where plans are underway to establish a Tinnitus Center in cooperation with the School of Audiology and Speech Pathology within the Faculty of Medicine at the University of Montreal. This «Center of Excellence» will permit the audiologists to offer a full range of interventions including preventive measures, diagnosis and treatments of all aspects associated with tinnitus (impairment, handicap and disability as developed by the C.I.D.I.H. and the WHO) [4].

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