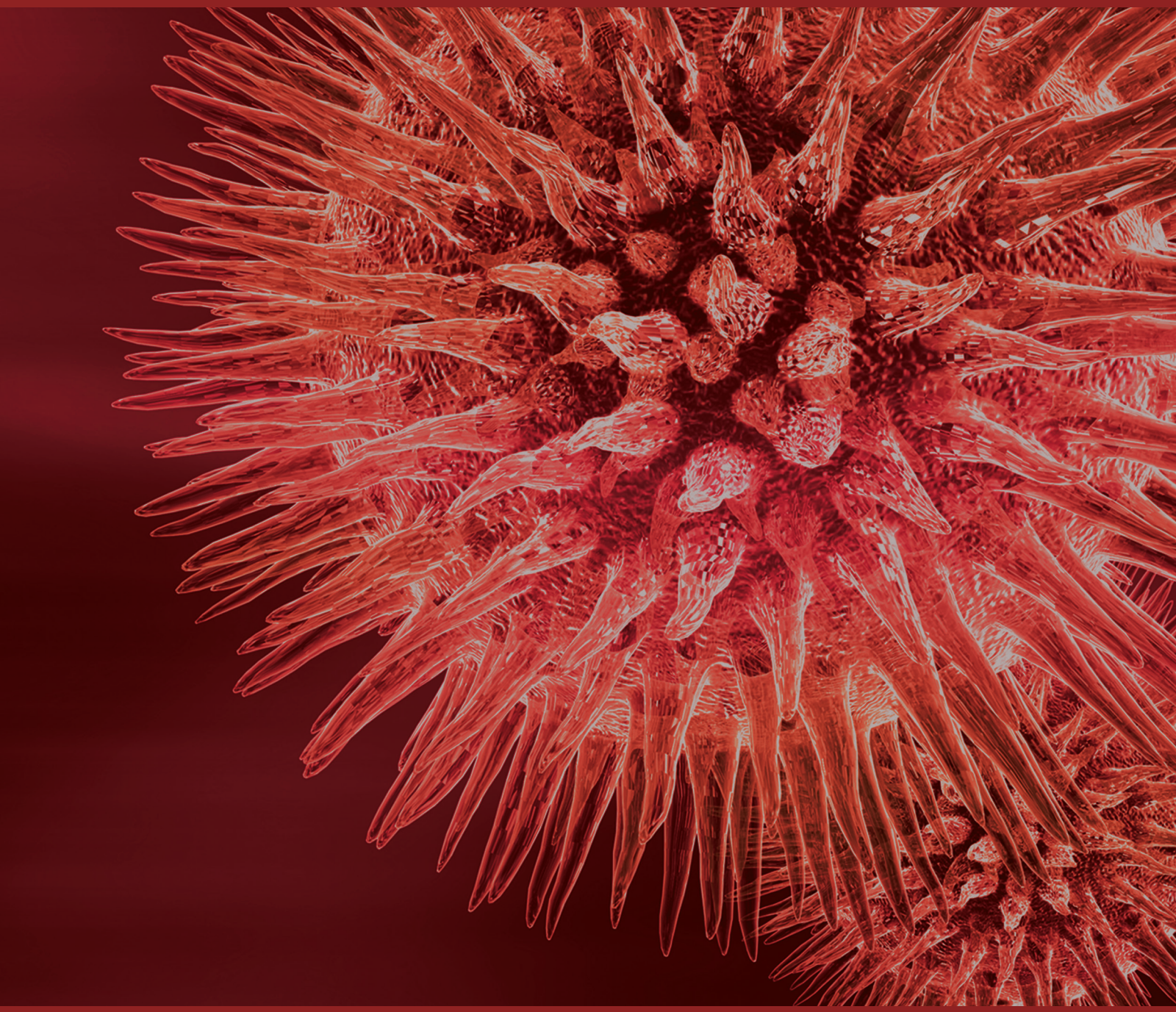
BioMed Research International

Pathology of Tinnitus and Hyperacusis-Clinical Implications

Guest Editors: Aage R. Moller, Richard Salvi, Dirk De Ridder, Tobias Kleinjung, and Sven Vanneste



Pathology of Tinnitus and Hyperacusis-Clinical Implications

BioMed Research International

Pathology of Tinnitus and Hyperacusis-Clinical Implications

Guest Editors: Aage R. Moller, Richard Salvi, Dirk De Ridder, Tobias Kleinjung, and Sven Vanneste

Contents

Hindawi Publishing Corporation
BioMed Research International
Volume 2015, Article ID 608437, 2 pages
http://dx.doi.org/10.1155/2015/608437

Editorial

Pathology of Tinnitus and Hyperacusis-Clinical Implications

Aage R. Moller,[1] Richard Salvi,[2] Dirk De Ridder,[3] Tobias Kleinjung,[4] and Sven Vanneste[1]

[1]*The University of Texas, Richardson, TX 75080, USA*
[2]*University of Buffalo, Buffalo, NY 14214, USA*
[3]*University of Otago, Dunedin 9016, New Zealand*
[4]*University of Zürich, Zürich, CH 8091, Switzerland*

Correspondence should be addressed to Aage R. Moller; amoller@utdallas.edu

Received 13 September 2015; Accepted 13 September 2015

Not long ago, tinnitus and hyperacusis were considered intractable symptoms and the lack of interest and shortage of research in diseases with these symptoms would have made publishing a special issue on tinnitus and hyperacusis nearly impossible. During the past two decades, there has been an explosion of research on tinnitus and incremental growth on hyperacusis, a condition associated with hearing loss, autism, migraine, closed head injuries, Williams syndrome, fibromyalgia, and other sensory hypersensitivity disorders. Prior to 1980, a search of PubMed turned up fewer than 25 publications with tinnitus in the title (Figure 1); the situation for hyperacusis was even more dismal with less than 5 publications in 1980 and only 19 in 2014.

This increase in publications reflects a large increase in research made possible by new hypotheses about the pathology of these diseases, advances in neuroscience in general, and new technological approaches. The increase in research funding by private philanthropic organizations such as the American Tinnitus Association, the Tinnitus Research Consortium, the Tinnitus Research Initiative, and Action on Hearing Loss has been essential for the progress in understanding of tinnitus and hyperacusis and the treatment of these disorders. Research grants from governmental agencies have also contributed to these advances in research regarding tinnitus and hyperacusis.

The incentive for this special issue was the tremendous personal, social, and financial costs associated with tinnitus and hyperacusis. For those suffering from severe or debilitating tinnitus or hyperacusis, the psychosocial and emotional costs can be enormous. While tinnitus and hyperacusis can affect anyone, young or old, those serving in the military are at a higher risk than nonmilitary people. Roughly 50% of combat personnel in the Gulf War developed tinnitus where exposure to intense noise and stress were likely the major contributing factors. Tinnitus ranks as the #1 service-connected disabilities in the Veterans Health Care System with compensation costs $1.2 billion for the year 2012, projected to reach $3 billion for the year 2017.

The completion of this special issue is a testament to the tremendous efforts by research groups around the world to develop a better understanding of the neural mechanisms underlying tinnitus and hyperacusis and to develop better and more effective therapies. This special issue combines association studies (tinnitus and sleep, tinnitus and headaches, tinnitus and interoceptive awareness, mastoid pneumatization, and pulsatile tinnitus), diagnostic studies (how to measure hyperacusis, the relevance of high-frequency hearing loss in tinnitus), and treatment studies (coordinated reset acoustic stimulation, repeated rTMS sessions).

A few highlights from the accepted papers in this special issue are discussed below.

(i) Hearing loss, which reduces the neural input to the central auditory system, is thought to be one of the major triggers for inducing tinnitus and aberrant neural activity within the brain; however, many people with tinnitus have normal hearing thresholds within the conventional audiometric range (0.25–8 kHz). The work of V. Vielsmeier et al. shows that many people with tinnitus who have what is regarded to

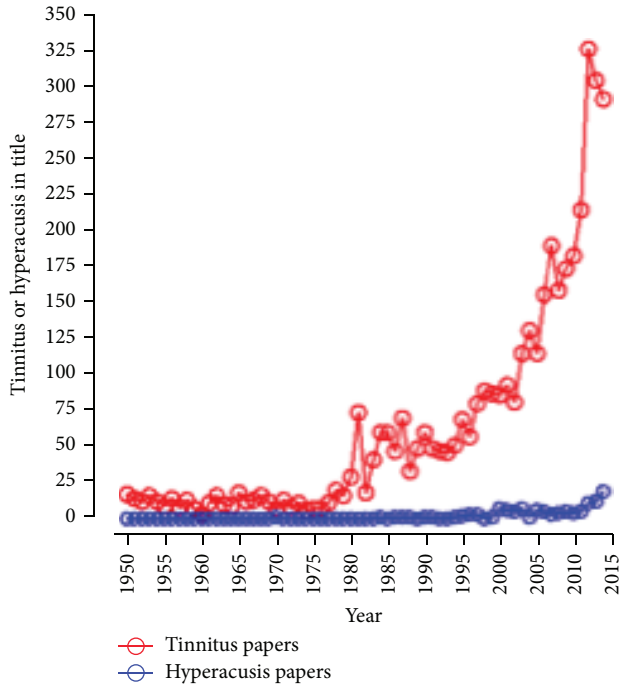


Figure 1: A search of PubMed shows an exponential increase of publications related to tinnitus over the last 20 years, while research related to hyperacusis has been mainly overlooked.

be normal hearing have elevated hearing thresholds above 8 kHz, which are strongly correlated with the laterality of the tinnitus. The take home message is that high-frequency audiometry should be an integral part of a comprehensive tinnitus assessment.

(ii) Some evidence suggests that the air spaces within the temporal bone (pneumatization) may contribute to the severity of pulsatile tinnitus. Using imaging techniques to quantify pneumatization, W. Liu et al., however, found little correlation between the severity of tinnitus and the degree of pneumatization.

(iii) While many people with tinnitus have hearing loss, not everybody who has hearing loss has tinnitus, a result that supports other findings that show that tinnitus is a multifactorial disease. The article by B. Langguth et al. present evidence that tinnitus and headache may be pathologically linked, consistent with earlier research linking tinnitus and hyperacusis to migraine.

(iv) Sleep disturbances are common in people with tinnitus but the relationship between sleep disturbance and the severity of a person's tinnitus has been unclear. M. Schecklmann et al. report that tinnitus distress is highly correlated with sleep disturbances.

(v) Over the past decade, many new and promising therapeutic approaches for treating tinnitus have emerged. Many different sound therapies designed to modify neural activity in the brain have been developed and remain to be validated. The exciting paper by C. Hauptmann et al. suggests that acoustic coordinated reset neuromodulation could become a therapeutic strategy for treating patients with chronic tonal tinnitus. Even though the lack of a control group does not permit showing real efficacy, the promising results of this open label study demonstrate that further controlled studies are warranted.

(vi) Another approach to treating people with tinnitus is repetitive transcranial magnetic stimulation (rTMS). One of the main problems with published studies of the use of rTMS to treat people with tinnitus is the small effect size and the fact that the effect of rTMS in tinnitus is limited in time. In a paper in this issue A. Lehner et al. demonstrate that repeating the rTMS sessions seems to be beneficial when the tinnitus distress worsens after waning of the rTMS effect.

(vii) The Hyperacusis Questionnaire is a tool used by clinicians to evaluate hyperacusis symptoms in tinnitus patients. Factor analysis of data obtained by K. Fackrell et al. suggests that only 10 items and two factors (attentional and social) in the Hyperacusis Questionnaire may be a more appropriate approach for assessing hyperacusis instead of the current 12 items and 3 factors (emotional, attentional, and social).

(viii) Furthermore, it was shown by M. Schecklmann et al. that using only 2 questions can give a good hint at whether hyperacusis is present: (1) Do you have a problem tolerating sounds because they often seem much too loud? (2) Do sounds cause you pain or physical discomfort?

(ix) P. Lau et al. demonstrate that tinnitus is unrelated to interoceptive awareness but that people with tinnitus tend to overestimate physical changes in comparison to people who do not have tinnitus.

In summary, special issues like this, covering clinical, diagnostic, and treatment aspects of tinnitus and hyperacusis, remain highly needed to continue the quest for finding better and more effective ways to treat these elusive symptoms. Only a better understanding of the causes of both tinnitus and hyperacusis and their pathology can pave the way to reaching this goal.

Aage R. Moller
Richard Salvi
Dirk De Ridder
Tobias Kleinjung
Sven Vanneste

Hindawi Publishing Corporation
BioMed Research International
Volume 2015, Article ID 970613, 4 pages
http://dx.doi.org/10.1155/2015/970613

Clinical Study

Temporal Bone Pneumatization and Pulsatile Tinnitus Caused by Sigmoid Sinus Diverticulum and/or Dehiscence

Liu Wenjuan,[1,2] Liu Zhaohui,[3] Zheng Ning,[2] Zhao Pengfei,[1] Dong Cheng,[1] and Wang Zhenchang[1]

[1]*Department of Radiology, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China*
[2]*Department of Radiology, Jining No. 1 People's Hospital, Shandong 272002, China*
[3]*Department of Radiology, Beijing Tongren Hospital, Capital Medical University, Beijing 100730, China*

Correspondence should be addressed to Liu Zhaohui; lzhtrhos@163.com and Wang Zhenchang; cjr.wzhch@vip.163.com

Received 3 March 2015; Accepted 21 April 2015

Academic Editor: Tobias Kleinjung

Background. Although air cells within temporal bone may play an important role in the transmission of pulsatile tinnitus (PT) noise, it has not been studied systematically. *Purpose*. To evaluate the difference in temporal bone pneumatization between PT patients with sigmoid sinus diverticulum and/or dehiscence (SSDD) and healthy people. *Material and Methods*. A total of 199 unilateral persistent PT patients with SSDD and 302 control subjects underwent dual-phase contrast-enhanced CT (DP-CECT), to assess the grade of temporal bone pneumatization in each ear. *Results*. In the bilateral temporal bone of 302 controls, 16 ears were grade I, 53 were grade II, 141 were grade III, and 394 were grade IV. Among the affected ears of 199 PT cases, 1 ear was grade I, 18 were grade II, 53 were grade III, and 127 were grade IV. There was no significant difference in the pneumatization grade between the affected PT ear and either ear in the healthy subjects ($p > 0.05$). *Conclusion*. Although air cells within the temporal bone are an important factor in the occurrence of PT, its severity does not differ significantly from the pneumatization of healthy people.

1. Introduction

Tinnitus is a common otologic symptom affecting 30% of the population worldwide [1]. Approximately 4% of patients have pulsatile tinnitus (PT), defined as the perception of somatosounds synchronized with the pulse in the absence of an external acoustic stimulus [2]. The psychological impact of PT on many patients is so severe that it can lead to depression or even suicide [3]. Although PT has numerous causes, sigmoid sinus diverticulum and/or dehiscence (SSDD) is the most frequent and treatable cause [4–10]. Some studies report that SSDD is the cause of PT in up to 20% of cases [5, 8, 9].

The mechanism of PT caused by SSDD remains unclear. Many studies have suggested that sound in the sigmoid sinus or vibration of the sigmoid wall caused by blood flow is transmitted to the inner ear through the dehiscent sigmoid sinus plate and air cells within the temporal bone, which is ultimately sensed as PT [8, 10, 11]. Thus, the air cells within the temporal bone may be an important contributor to PT occurrence. However, the magnitude of temporal bone pneumatization necessary to trigger PT and the difference between PT patients and healthy people, which is critical to the etiological diagnosis and may affect therapeutic planning, is still debated at present. Some studies suggest that the diffused pneumatization in temporal bone and the pneumatization in patients with PT caused by the internal carotid artery (ICA) were greater than those observed in healthy people and may be an important contributor to PT. Sözen et al. [12] evaluated the relationship between subjective PT and petrous bone pneumatization by comparing 25 PT patients with healthy individuals. They detected petrous bone pneumatization in 22 (68.8%) of 32 ears with subjective PT, which was statistically higher than the prevalence in control subjects (24%). By contrast, a different study found that 80% of PT patients with sigmoid sinus diverticulum exhibited hyperpneumatization or good pneumatization of the temporal bone, while 20% of their patient sample exhibited moderate pneumatization of the temporal bone [11].

The aim of this study was to evaluate the temporal bone pneumatization in PT caused by SSDD by comparing patients diagnosed with PT and healthy control subjects. We hypothesized that the temporal bone pneumatization of the PT group was greater than the pneumatization in the control subjects.

2. Materials and Methods

2.1. Subjects. The Hospital Institutional Review Board for Human Subjects Research approved this study. We evaluated the pneumatization of temporal bone in the unilateral PT group and control group. The PT group included 199 SSDD patients comprising 18 male and 181 female diagnosed with unilateral PT between May 2008 and January 2013. Sixty-five patients had left PT, and 134 had right PT. The duration of PT was 3 months to 36 years. All patients were diagnosed with SSDD using dual-phase contrast-enhanced computed tomography (DP-CECT) of the temporal bone, and other causes of PT, which was proven by imaging examination and other clinical examination, such as aberrant internal carotid artery, abnormal emissary vein, dural arteriovenous fistula, benign intracranial hypertension, carotid atherosclerosis, paraganglioma, high-riding or dehiscent jugular bulb, or otosclerosis, were excluded. Thirty-eight patients suffering severe and continuous tinnitus underwent surgery of sinus wall reconstruction. Among them, the PT resolved completely in 29 patients and decreased significantly in the remaining 9 patients. Among 937 consecutive patients with orbital tumors, paranasal sinus tumors, or orbital trauma undergoing DP-CECT between May 2008 and January 2013 who did not have a history of tinnitus, we identified 302 patients (209 male and 93 female) as controls after excluding patients undergoing brain surgery or those with low-quality images, temporal bone fracture, and other ear pathologies.

2.2. Imaging Method. DP-CECT was performed in all patients using a 64-slice multidetector CT (Brilliance 64; Philips, Best, Netherlands) at the following parameters: 120 kVp, 300 mA, detector collimation 64 × 0.625 mm, rotation time 0.75 s, pitch 0.89 : 1, matrix 512 × 512, and field-of-view (FOV) 22 × 22 cm. The scan range was from the vertex to the sixth cervical vertebrae. Iodinated nonionic contrast agent (Iopamidol (370 mg iodine/mL); Bracco, Shanghai, China) was administered at 5 mL/s using an electric power injector. The contrast agent was dosed at 1.5 mL/kg according to the patient's weight in all subjects. The ascending aorta served as the trigger point, the trigger area measured 200 mm^2, and the trigger threshold was set at 150 HU. The arterial phase was triggered by the Bolus-Tracking program (Trigger Bolus software; Philips, Best, Netherlands) after administering the contrast agent and performed in the cephalocaudal direction. The arterial phase time ranged from 8 to 12 s. The venous phase scan was performed in the opposite direction after a fixed 8 s delay. All arterial phase images were reconstructed by standard algorithms, and standard and bone algorithms were used in all venous phase images.

2.3. Image Interpretation. The CT images were reviewed by two radiologists (LZH and LWJ, with 13 and 11 years of experience, resp.), and the findings were determined by consensus. SSDD was diagnosed according to the following previously described criteria: incomplete thin bone surrounding the sigmoid sinus and/or a diverticulum entering the mastoid bone [5, 6, 13].

The temporal bone pneumatization was classified according to the method described by Han et al. [14]. The sigmoid sinus was the designated reference for evaluation. On the image in which the malleoincudal complex resembled an ice cream cone-shape, three parallel lines angled 45° anterolaterally were applied so that one line crossed the most anterior point of the sigmoid sinus at its junction with the petrous bone, the second line crossed the most lateral margin along the transverse plane of the sigmoid groove, and the third line crossed the most posterior point of the sigmoid sinus, respectively. The magnitude of temporal bone pneumatization was classified into four categories as follows: grade I (hypopneumatization), the pneumatization remained anteromedial to the line drawn at the most anterior point of the sigmoid sinus; grade II (moderate pneumatization), the pneumatization extended into the space between the two lines at the most anterior and lateral aspects of the sigmoid sinus; grade III (good pneumatization), the pneumatization extended to the space between the two lines at the most lateral and posterior aspects of the sigmoid sinus; and grade IV (hyperpneumatization), the pneumatization extended posterolaterally beyond the line drawn at the most posterior point of the sigmoid sinus.

2.4. Data Analysis and Statistics. All statistical analyses were performed using statistical software (SPSS, version 16.0; SPSS, Chicago, IL USA), and a p value less than 0.05 was considered statistically significant. The χ^2 test was used initially to analyze the control group according to laterality and gender. The independent t-test was then used to access the PT and control groups according to age. If there were no differences in the pneumatization grade between each lateral side and gender in the control group, and the patient ages could be matched between the two groups, then the χ^2 test was used to analyze the proportional data between the affected side of the PT patients and the control subjects.

3. Results

Tables 1 and 2 list the temporal bone pneumatization grade per lateral side and gender, respectively, in the control group. There was no significant difference according to laterality ($p = 0.471$) or gender ($p = 0.775$).

The PT group included 199 PT patients with a mean age of 40.6 ± 13.8 years (range 17–77 years), and the control group included 302 patients with a mean age of 40.8 ± 11.7 years (range 13–80 years). There was no significant difference in age between the PT and control groups ($p = 0.865$).

As shown in Table 3, there was no significant difference in the pneumatization grade between the affected side in the PT group and either side in the control group ($p = 0.263$).

Table 1: Comparison of temporal bone pneumatization grade between left and right ears in control group.

Pneumatization grade	Side (number of ears)		Statistical analysis	
	Left	Right	χ^2	p
I	8	8		
II	22	31		
III	67	74	2.526	0.471
IV	205	189		
Total	302	302		

Table 2: Comparison of temporal bone pneumatization grade by gender in control group.

Pneumatization grade	Gender (number of ears)		Statistical analysis	
	Male	Female	χ^2	p
I	12	4		
II	39	14		
III	94	47	1.157	0.775
IV	273	121		
Total	418	186		

Table 3: Comparison of temporal bone pneumatization grade between the PT and control groups.

Pneumatization grade	Group (number of ears)		Statistical analysis	
	PT side	Control	χ^2	p
I	1	16		
II	18	53		
III	53	141	3.986	0.263
IV	127	394		
Total	199	604		

PT: pulsatile tinnitus.

4. Discussion

Our study found that the temporal bone pneumatization grade in patients with PT was identical to the grade in healthy people. Additionally, although sigmoid plate dehiscence has been reported as a cause of PT, we found that it also occurs in some healthy people. Therefore, abnormal blood flow within the sigmoid sinus is the essential factor triggering PT. Only when abnormal sigmoid sinus perfusion, sigmoid plate dehiscence, and normal temporal bone pneumatization coexist will PT potentially occur.

Approximately 90.5% of the temporal bone pneumatization lesions were grades II and IV (good pneumatization and hyperpneumatization), which supports the theory that extensive temporal bone pneumatization favors sound transmission, as suggested by others. Large air cells increase the resonance of sound and serve as an amplifier. Increased transmission of normal perfusion sounds to the cochlea would lead to PT [15, 16]. However, 9.5% of temporal bone pneumatization in the patient population were grades I and II (hypopneumatization and moderate pneumatization). Multiple small air cells in poorly pneumatized temporal bone do not augment the resonance of blood flow vibration in the sigmoid sinus. However, the transmission distance from the sigmoid sinus to the inner ear is shorter than in extensively pneumatized temporal bone and therefore may be sensed as PT.

In our study, DP-CECT was used to examine the detailed anatomic structure and accurately diagnose PT caused by SSDD. DP-CECT includes arterial and venous phases and can demonstrate the status of vessels and temporal bones simultaneously in a single study. Krishnan et al. [17] suggested that DP-CECT can effectively detect arterial, venous, and inner ear causes of PT in a prospective study of 16 PT patients. Han et al. [14] classified the temporal bone pneumatization into grades I–IV based on the sigmoid sinus, which can be used to assess pneumatization with good feasibility. The method used a single CT image and assessed the structure of the sigmoid sinus, which was found to accurately represent pneumatization in the entire temporal bone. In our study, we chose this method to classify the temporal bone pneumatization because it was simple and practical for a large sample analysis.

Notably, our study is a retrospective study, and the difference in temporal bone pneumatization was analyzed between PT patients and healthy subjects. However, the specific mechanism generating the air cells within the temporal bone in PT was not examined and warrants further experimental study.

5. Conclusion

The magnitude of temporal bone pneumatization does not significantly differ between PT patients with SSDD and healthy people, which indicates that normal pneumatized temporal bone can potentially meet the criteria of SSDD required to induce PT.

Disclosure

Liu Wenjuan and Liu Zhaohui are co-first authors.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

This work was supported by Grant nos. 81171311 and 81371545 from the National Natural Science Foundation of China and Grant no. 13JL03 from Capital Medical University, China.

References

[1] A. J. Heller, "Classification and epidemiology of tinnitus," *Otolaryngologic Clinics of North America*, vol. 36, no. 2, pp. 239–248, 2003.

[2] J. L. Stouffer and R. S. Tyler, "Characterization of tinnitus by tinnitus patients," *Journal of Speech and Hearing Disorders*, vol. 55, no. 3, pp. 439–453, 1990.

[3] S. Pridmore, G. Walter, and P. Friedland, "Tinnitus and suicide: Recent cases on the public record give cause for reconsideration," *Otolaryngology—Head and Neck Surgery*, vol. 147, no. 2, pp. 193–195, 2012.

[4] F. Signorelli, K. Mahla, and F. Turjman, "Endovascular treatment of two concomitant causes of pulsatile tinnitus: sigmoid sinus stenosis and ipsilateral jugular bulb diverticulum. Case report and literature review," *Acta Neurochirurgica*, vol. 154, no. 1, pp. 89–92, 2012.

[5] D. J. Eisenman, "Sinus wall reconstruction for sigmoid sinus diverticulum and dehiscence: a standardized surgical procedure for a range of radiographic findings," *Otology and Neurotology*, vol. 32, no. 7, pp. 1116–1119, 2011.

[6] D. E. Mattox and P. Hudgins, "Algorithm for evaluation of pulsatile tinnitus," *Acta Oto-Laryngologica*, vol. 128, no. 4, pp. 427–431, 2008.

[7] A. K. Grewal, H. Y. Kim, R. H. Comstock III, F. Berkowitz, H. J. Kim, and A. K. Jay, "Clinical presentation and imaging findings in patients with pulsatile tinnitus and sigmoid sinus diverticulum/dehiscence," *Otology and Neurotology*, vol. 35, no. 1, pp. 16–21, 2014.

[8] J. Xue, T. Li, X. Sun, and Y. Liu, "Focal defect of mastoid bone shell in the region of the transverse-sigmoid junction: a new cause of pulsatile tinnitus," *The Journal of Laryngology & Otology*, vol. 126, no. 4, pp. 409–413, 2012.

[9] K. J. Otto, P. A. Hudgins, W. Abdelkafy, and D. E. Mattox, "Sigmoid sinus diverticulum: a new surgical approach to the correction of pulsatile tinnitus," *Otology and Neurotology*, vol. 28, no. 1, pp. 48–53, 2007.

[10] G.-P. Wang, R. Zeng, Z.-H. Liu et al., "Clinical characteristics of pulsatile tinnitus caused by sigmoid sinus diverticulum and wall dehiscence: a study of 54 patients," *Acta Oto-Laryngologica*, vol. 134, no. 1, pp. 7–13, 2014.

[11] Z. Liu, C. Chen, Z. Wang et al., "Sigmoid sinus diverticulum and pulsatile tinnitus: analysis of ct scans from 15 cases," *Acta Radiologica*, vol. 54, no. 7, pp. 812–816, 2013.

[12] E. Sözen, I. Çelebi, Y. O. Uçal, and B. U. Coşkun, "Is there a relationship between subjective pulsatile tinnitus and petrous bone pneumatization?" *The Journal of Craniofacial Surgery*, vol. 24, no. 2, pp. 461–463, 2013.

[13] B. F. Branstetter and J. L. Weissman, "The radiologic evaluation of tinnitus," *European Radiology*, vol. 16, no. 12, pp. 2792–2802, 2006.

[14] S. J. Han, M. H. Song, J. Kim et al., "Classification of temporal bone pneumatization based on sigmoid sinus using computed tomography," *Clinical Radiology*, vol. 62, pp. 1110–1118, 2007.

[15] M. Tüz, H. Doğru, and A. Yeşildağ, "Subjective pulsatile tinnitus associated with extensive pneumatization of temporal bone," *Auris Nasus Larynx*, vol. 30, no. 2, pp. 183–185, 2003.

[16] O. Topal, S. S. Erbek, S. Erbek, and L. N. Ozluoglu, "Subjective pulsatile tinnitus associated with extensive pneumatization of temporal bone," *European Archives of Oto-Rhino-Laryngology*, vol. 265, no. 1, pp. 123–125, 2008.

[17] A. Krishnan, D. E. Mattox, A. J. Fountain, and P. A. Hudgins, "CT arteriography and venography in pulsatile tinnitus: preliminary results," *The American Journal of Neuroradiology*, vol. 27, no. 8, pp. 1635–1638, 2006.

Hindawi Publishing Corporation
BioMed Research International
Volume 2015, Article ID 487372, 9 pages
http://dx.doi.org/10.1155/2015/487372

Research Article

The Relevance of Interoception in Chronic Tinnitus: Analyzing Interoceptive Sensibility and Accuracy

Pia Lau,[1] Miriam Miesen,[1,2] Robert Wunderlich,[1,3] Alwina Stein,[1] Alva Engell,[1] Andreas Wollbrink,[1] Alexander L. Gerlach,[4] Markus Junghöfer,[1] Thomas Ehring,[5] and Christo Pantev[1]

[1]*Institute for Biomagnetism and Biosignalanalysis, University Hospital of Münster, Malmedyweg 15, 48149 Münster, Germany*
[2]*Institute of Psychology, University of Münster, Fliednerstraße 21, 48149 Münster, Germany*
[3]*Institute for Physiological Psychology, University of Bielefeld, Universitätsstraße 25, 33615 Bielefeld, Germany*
[4]*Institute of Clinical Psychology and Psychotherapy, University of Cologne, Pohligstraße 1, 50969 Cologne, Germany*
[5]*Department of Psychology, LMU Munich, Leopoldstraße 13, 80802 Munich, Germany*

Correspondence should be addressed to Christo Pantev; pantev@uni-muenster.de

Received 17 April 2015; Accepted 22 July 2015

Academic Editor: Aage R. Møller

In order to better understand tinnitus and distress associated with tinnitus, psychological variables such as emotional and cognitive processing are a central element in theoretical models of this debilitating condition. Interoception, that is, the perception of internal processes, may be such a psychological factor relevant to tinnitus. Against this background, 20 participants suffering from chronic tinnitus and 20 matched healthy controls were tested with questionnaires, assessing interoceptive sensibility, and participated in two tasks, assessing interoceptive accuracy: the Schandry task, a heartbeat estimation assignment, and a skin conductance fluctuations perception task assessing the participants' ability to perceive phasic increases in sympathetic activation were used. To test stress reactivity, a construct tightly connected to tinnitus onset, we also included a stress induction. No differences between the groups were found for interoceptive accuracy and sensibility. However, the tinnitus group tended to overestimate the occurrence of phasic activation. Loudness of the tinnitus was associated with reduced interoceptive performance under stress. Our results indicate that interoceptive sensibility and accuracy do not play a significant role in tinnitus. However, tinnitus might be associated with a tendency to overestimate physical changes.

1. Introduction

Tinnitus affects up to 40% of the population in Western countries at least temporarily [1]. One to three percent of the general population report a significant reduction in their quality of life due to their tinnitus, for example, through its effect on sleep and/or mood [2]. It is widely assumed that tinnitus is a result of maladaptive cortical plasticity [3]. Yet psychological constructs are believed to mediate this process and are especially tied to the distress perceived because of the tinnitus [4–6]. Current psychological models of tinnitus assume a neuronal basis of the tinnitus and in addition focus on the interplay of different psychological processes explaining the perceived distress [7]. For example, McKenna et al. [7] propose that tinnitus distress starts with the detection of tinnitus. Then, a vicious cycle of negative automatic thoughts, detrimental safety behaviors, selective attention, and monitoring is triggered. This model draws distinctively from models of other mental disorders such as panic disorder. In the case of panic attacks, small internal changes, for example, of the heartbeat, trigger a similar dysfunctional circuit and in the end result in panic attacks (cf. [8]) Hence, one risk factor for panic disorder is interoception [9]. Interoception is defined as sensitivity to internal stimuli which originate from the body itself [10]. Interoception is also connected to other mental disorders, including general anxiety disorder, bulimia nervosa, anorexia nervosa, and somatoform disorders [11–14]. In addition, interoception has been shown to be linked

to psychological variables, such as emotional experience, emotional memory processes, and alexithymia [14–16], which are also discussed in the context of tinnitus (e.g., [17, 18]).

Tinnitus *per se* is a process of interoception as it is attention toward internal percept. Whether interoception can be assumed to be a dysfunctional factor for chronic tinnitus however is still obscure. Next to the overlap of etiological models, psychotherapeutic aspects for mental disorders and tinnitus have common characteristics: an important intervention in evidence-based treatment of panic disorder is interoceptive exposure, which includes purposely evoking internal stimuli (e.g., hyperventilating and running steps to increase the heartbeat) in order to make the patients learn that those internal signals are not harmful [19]. Similarly, intentionally focusing on the tinnitus is a strategy used in current treatments for tinnitus [20]. This intervention showed a significant reduction in tinnitus related distress [21] which points towards a meaningful connection between interoception and chronic tinnitus.

More evidence for a connection between chronic tinnitus and interoception comes from the field of neuroscience: the right anterior insula is activated in interoceptive processes likewise in tinnitus sufferers, especially if they are highly distressed [22–26]. Taken together, the current research concerning tinnitus offers hints for a connection between chronic tinnitus and interoception, but this question has never been addressed directly. Hence, this study can be seen as a first step towards a better understatement of the putative role of interoception in tinnitus.

Current research suggests that interoception exhibits a threefold structure: interoceptive sensibility, accuracy, and awareness [27]. Interoceptive sensibility is regarded as the subjective perception of interoception measured through questionnaires or interviews. Interoceptive accuracy, sometimes also named sensitivity, is the objective measurement of the accurate detection of internal processes. Finally, interoceptive awareness is described as higher-order component in interoception and covers more a metacognitive understanding of interoception, for example, the knowledge about the accuracy of the own interoceptive perception. As the latter is difficult to measure (cf. [28]) and our study focused on the basic aspects of interoception, we collected data on the first two components, namely, interoceptive sensibility and accuracy.

A standard procedure to operationalize interoceptive accuracy is using the Schandry task [29]. Participants have to report on all heartbeats felt during a signaled period of time. The participants have to rely solely on their feeling while no auxiliary means are allowed. To also account for the accuracy of the perception of internal stimuli other than the heartbeat, Andor et al. [30] introduced a novel interoceptive accuracy task looking at the perception of spontaneous skin conductance fluctuations. In this task, phases with stable skin conductance (no nonspecific skin conductance fluctuations) thus representing the absence of internal arousal, as well as nonspecific skin conductance fluctuations (NSCF), representing current phasic sympathetic arousal, are recorded. Participants have to decide if an acoustic signal was preceded by either phasic arousal or a period of stable skin conductance. This method allows the use of signal detection methodology and thus the calculation of a perception bias to estimate whether participants spuriously perceive bodily symptoms (cf. Katzer et al. [31] for the concept of illusory bodily symptoms and its relevance to the understanding of somatic symptom disorder).

In an attempt to explore interoception as clinically relevant construct to tinnitus, we conducted an *a priori* power analysis based on effect sizes from a review paper on anxiety disorders [32]. Sample size was chosen to be able to detect a momentous, clinically relevant difference between the groups. We reasoned that, in order to establish interoception in tinnitus as a valid and meaningful construct, effect sizes should be comparable to, for example, panic disorder.

A multimethod assessment of interoception, including interoceptive sensibility through questionnaire measures and interoceptive accuracy through the Schandry task and the skin conductance task, was used. We hypothesized that a group with tinnitus sufferers exhibits higher levels of interoceptive sensibility and accuracy compared to a group of healthy controls. Based on findings in studies trying to better understand somatic symptom disorder such as health anxiety [28], we also expected an interoceptive bias and postulated that the tinnitus group shows a more liberal bias towards the perception of internal processes, for example, phasic sympathetic arousal, irrespective of its actual occurrence.

Tinnitus sufferers regularly associate stress with tinnitus [33]. For example, in a study by Baigi et al. [34], stress was related to worsening of the tinnitus. Hébert and Lupien [35] found higher cortisol levels in a tinnitus group compared to a control group after stress induction. Since stress appears to be associated with tinnitus, we hypothesized that the tinnitus group shows higher interoceptive accuracy under induced stress, whereas the performance of the control group should be less affected. To rule out a better performance based on an increased cardiac output due to the stress, we included a control condition where the participants had to reach elevated levels of cardiac output through movement on an ergometer.

2. Methods and Materials

2.1. Participants. Groups were matched with respect to age, gender, and level of education. Unexpectedly, the groups differ in the Body Mass Index (BMI) (Table 1). The study protocol was approved by the ethics committee of the Department of Psychology at the University of Münster and was conducted according to the Declaration of Helsinki. Recruitment was conducted through advertisements in local newspapers, an announcement on the institute's website, and the distribution of information brochures and posters throughout the university and in different locations in town. Participants were paid 20€ for their attendance. Exclusion criteria were high blood pressure, cardiac diseases, asthma, and pregnancy as the stress induction might have been disadvantageous for individuals showing any of these conditions. Pulsatile tinnitus, medication with cardiovascular or psychopharmacological effects, and any diagnosis of mental disorder were additional exclusion criteria. The absence of

Table 1: Demographic description and mean scores of the questionnaires of tinnitus group and control group.

	Tinnitus group ($n = 20$)		Control group ($n = 20$)		$t(38)$	p
	M	SD	M	SD		
Age (in Years)	42.8	13.1	41.7	12.9	0.26	0.80
BMI (kg/m^2)	25.0	3.9	22.3	3.2	2.32	0.03*
Physical exercise per week (hours)	3.6	2.5	3.9	2.8	−0.34	0.74
Baseline heart rate (beats per minute)	75.8	15.7	70.3	11.9	1.26	0.22
BAQ	68.75	11.67	65.60	16.37	−0.70	0.24
PBCS	11.95	3.734	11.85	4.32	−0.08	0.47
MAIA	3.00	0.39	2.91	0.54	−0.61	0.27
SOMS	59.05	10.11	58.65	11.87	−0.46	0.65
PANAS-PA	30.65	5.68	31.50	6.09	0.43	0.67
PANAS-NA	11.85	1.39	11.55	2.84	0.12	0.91
THQ	22.18	16.01	—	—		
THI	23.80	13.73	—	—		

BMI: Body Mass Index, BAQ: Body Awareness Questionnaire, PBCS: Private Body Consciousness Scale, MAIA: Multidimensional Assessment of Interoceptive Awareness, SOMS: Screening for Somatoform Disorders, PANAS-PA: Positive Affect Scale of the Positive and Negative Affect Scale, PANAS-NA: Negative Affect Scale of the Positive and Negative Affect Scale, THQ: Tinnitus Handicap Questionnaire, THI: Tinnitus Handicap Inventory, * $p < 0.05$.

mental disorders was ensured by assessing all participants with the structured clinical interview for mental disorders for DSM-IV (SCID, German version; [36]).

2.2. Procedure. All potential participants were prescreened for the above-mentioned exclusion criteria via telephone. An e-mail including the study information sheet was sent to individuals meeting all inclusion criteria. On the day of the appointment, each participant gave written informed consent prior to participating in the experiments. The assessment started with the SCID to ensure absence of any mental disorder, which was the case for all participants.

2.2.1. Questionnaires. Following the suggestion by Mehling et al. [37], different questionnaires to assess interoceptive sensibility were utilized. We used the Body Awareness Questionnaire (BAQ, [38]), a scale covering the perception of nonemotive, normal body processes, for example, rhythms of the body and anticipating body reactions. Furthermore, we used the first questionnaire dealing with interoception: the Private Body Consciousness Scale (PBCS, [39]), which measures a disposition to focus on internal processes, a sensitivity for bodily changes, and the awareness of interoceptive feedback. Additionally we handed out the Multidimensional Assessment of Interoceptive Awareness (MAIA, [40]), an eight-dimensional questionnaire covering noticing, notdistracting, not-worrying, attention regulation, emotional awareness, self-regulation, body listening, and trusting. For all three questionnaires, reliability and valditiy could be shown [38, 41, 42]. Positive affectivity and negative affectivity were measured with the Positive and Negative Affect Scale (PANAS, [43]) and somatization with the Screening for Somatoform Disorders (SOMS-7T, [44]). The tinnitus group additionally completed the Tinnitus Handicap Questionnaire (THQ, [45]) and the Tinnitus Handicap Inventory (THI, [46]) to quantify their tinnitus distress as well as visual analogue scales (VAS) covering the topics of perceived loudness, annoyance, distress, and handicap of their tinnitus.

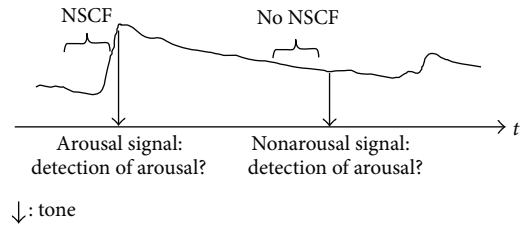


Figure 1: Description of the skin conductance task as measure of interoceptive accuracy as depicted in Andor et al. (2008). NSCF: nonspecific skin conductance fluctuation, t = time.

2.2.2. Skin Conductance Task. Skin conductance was measured with a Varioport (Becker Meditec, Karlsruhe, Germany) with a sampling rate of 16 Hz. Two silver/silver chloride electrodes with a contact surface area of 2 cm^2 to which isotonic paste was applied were used [47]. The electrodes were attached to the palm of the nondominant hand [48]. The Variotest system (Gerhard Mutz, Cologne, Germany) identified online periods of stable skin conductance (no NSCF) and periods of phasic sympathetic activation (NSCF), for a more detailed description: Andor et al. [30]. Participants were instructed to focus on their body arousal during the entire task and indicate, after each tone, whether a tone was preceded by an occurrence of body arousal (see Figure 1 for an illustration of the task procedure). The algorithm, whether the program was scanned for a stable phase or a fluctuation, was pseudorandomized with the restriction that the two different types of phases were not signaled more than two times in a row. The same sequence was used for

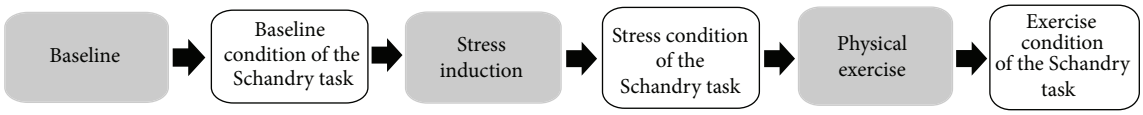


Figure 2: Procedure of the Schandry task.

all participants. The search window for a stable phase or a fluctuation was 150 s. If the intended event occurred within this time frame, the tone was presented; otherwise, no tone was presented and the program continued with the next trial. If more than five trials were missed, the subject was excluded from data analysis and the time window was shortened to 30 s. The latter intended to ensure that all participants started with the same feeling into the second task; for example, they did not notice that the task was cancelled. Usually participants are relaxed during this task and show only a few fluctuations in the skin conductance. In order to increase the arousal level of the participants, that is, provoke more fluctuations, two one-minute breaks were included in the task in which participants were asked to talk about their last vacation, book, or movie. As participants are usually more aroused in the beginning of an experimental session than in later phases, we chose to conduct the skin conductance task always first before the Schandry task.

2.2.3. Schandry Task. In the second task, interoceptive accuracy was measured using the Schandry task [29]. Participants were instructed to count their heartbeat for an indicated amount of time. The electrocardiogram (ECG) was measured with a technical device (NeXus-10 Mark II, Mind Media BV, Herten, Netherlands) using three silver/silver chloride electrodes attached to the torso according to Einthoven lead II. The ECG was sampled at a rate of 256 Hz. The trials were presented with Presentation (Neurobehavioral Systems Inc., Berkeley, CA, USA).

Three within-subject conditions existed for this task: a baseline condition with the classic Schandry task, a condition following a social stress induction, and a control condition following physical exercise on an ergometer (see Figure 2). Each condition consisted of five consecutive trials of different length (20, 25, 30, 35, and 40 s) which were presented in randomized order. After each trial, participants had 10 s to report their heartbeat count to the investigator. A 30-second pause followed each trial. The beginning and the end of each trial were marked by a tone (onset tone: 800 Hz, 300 ms; offset tone: 500 Hz, 300 ms).

Before the baseline Schandry task, participants were given five minutes to get used to the ECG and afterwards filled out the good-and-bad mood and agitation-tranquility scale of the Multidimensional Questionnaire of Mental State (Mehrdimensionaler Befindlichkeitsfragebogen, MDBF, [49], cf. [50]) to report on their current mental state. Afterwards, the Schandry task was presented. Participants were asked to sit upright with their back of the hands resting on their thighs. This and the explicit instruction to avoid any other auxiliary means (e.g., measuring the pulse with the fingertips) were intended to ensure that the participants relied on their interoception solely. One test trial was conducted to make the participants familiar with the task. Then, the baseline Schandry task with its five trials was presented, followed by the stress induction. Here the participants performed the cognitive stress task of the Trier Social Stress Test [51]. For five minutes, participants had to repeatedly subtract 13, starting at 1022. They were told to do this mental arithmetic task as fast and as accurate as possible. In case of an error, participants were interrupted and told to start again at 1022. To further increase stress, the investigator said "Please calculate faster." Moreover, participants were told that also the voice and the posture during this mathematical task would be analyzed and therefore he or she was videotaped during the task. To enhance stress levels through the additional factor of self-awareness, participants could see themselves on a screen. After the stress induction period, participants again filled out the MDBF. The second block of five trials of the Schandry task was presented, followed by another completion of the MDBF. Finally, the last condition of the Schandry task started: heartbeat perception after physical exercise (five minutes cycling on an ergometer). The investigator instructed the participant to either speed up or slow down their cycling to adjust their average heart rate to the heart rate measured in the stress induction phase. Finally, the third block of the Schandry task was conducted. At the end of the experiment participants were informed about the purpose of the experiment, including the function of the stress induction.

2.3. Analysis

2.3.1. Skin Conductance Task. According to participants' ability to detect NSCFs, the sensitivity index d' was calculated as follows: Z(hit rate) – Z(false alarm rate). If the hit rate equals the false alarms rate, the index is zero implicating low sensitivity. The higher d' is, the better the participants were able to detect phasic internal arousal correctly. Furthermore, an index to quantify bias C as response behavior was calculated: $-0.5 * (Z(\text{false alarm rate}) + Z(\text{hit rate}))$. It describes whether the participant had a conservative response behavior, that is, reporting more often no arousal than arousal, or a liberal one, that is, reporting more often arousal irrespective of its occurrence. The first is represented through an index higher than 0 and the latter below 0; an index around 0 reflects that there is no tendency, for example, a balanced answering behavior.

2.3.2. Schandry Task. Data from the NeXus (including the triggers from Presentation) was imported to the Polyman program (Bob Kemp & Marco Roessen, Den Haag, Netherlands) to quantify the participants' heartbeat. Based on this data (recorded heartbeat) and the answers given by the

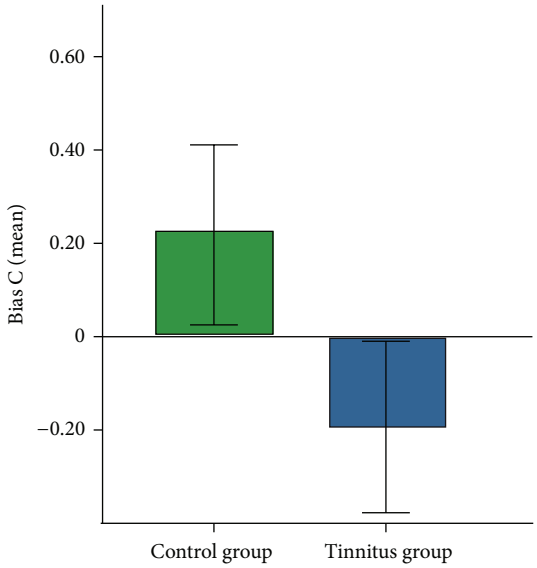


Figure 3: Mean score for bias C in the control and the tinnitus group. Error bars indicate the standard error.

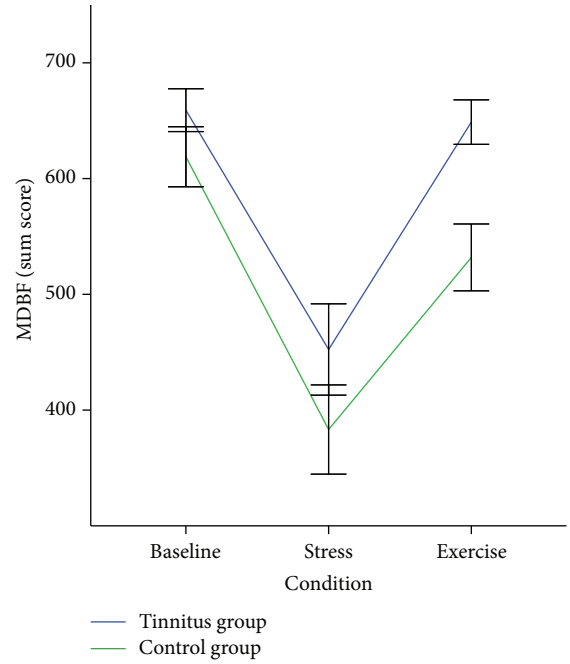


Figure 4: Current mood throughout the Schandry task conditions for both groups. Error bars indicate standard error. MDBF: Multidimensional Questionnaire of Mental State.

participants (counted heartbeat) during the experiment, the heartbeat perception score was calculated (HBP, HBP = 1 − 1/5 ∑(|recorded heartbeats − counted heartbeats|/recorded heartbeats), (cf. [11, 52, 53])). The better the performance, that is, the accuracy of the given answers, the higher the HBP. The maximal value is 1.

3. Results

Twenty participants with chronic tinnitus (M = 42.8 years, SD = 13.1, 40% female) and twenty healthy control participants without tinnitus (M = 41.7 years, SD = 12.9, 40% female) were tested. Groups were matched with respect to age, gender, and level of education. Unexpectedly, the groups differ in the Body Mass Index (BMI); see Table 1.

3.1. Questionnaires. The t-test for independent samples revealed no significant differences between the two groups regarding the self-report measures of interoception, BAQ: $t(38) = -0.70$, $p = 0.24$; PBCS: $t(38) = -0.08$, $p = 0.47$; MAIA: $t(38) = -0.61$, $p = 0.27$. The same is true for the SOMS, $t(38) = 0.12$, $p = 0.91$, PANAS-PA, $t(38) = -0.46$, $p = 0.65$, and PANAS-NA, $t(38) = 0.43$, $p = 0.67$ (see Table 1).

3.2. Skin Conductance Task. Due to too few spontaneous skin conductance fluctuations (less than 5), 12 participants had to be excluded from the analysis, yielding 15 participants in the tinnitus group and 13 in the control group. We found no difference of the sensitivity index d' between the groups in a t-test for independent samples, $t(26) = 0.59$, $p = 0.28$, and $d = 0.22$ (tinnitus group M = −0.14, SD = 1.30 and control group M = 0.16, SD = 1.51). A trend was found for the bias C: $t(26) = 1.53$, $p = 0.07$, $d = 0.58$ (see Figure 3, tinnitus group M = −0.19, SD = 0.71 and control group M = 0.22, SD = 0.70).

3.3. Schandry Task. All participants were included in the analysis. In order to check if we successfully implemented the three conditions we compared the three consecutive current mental state scores. A repeated measures ANOVA with the factors *Condition* (baseline versus stress versus exercise) and *Group* (tinnitus versus control) showed a significant difference between the three conditions, $F(2,76) = 53.12$, $p < 0.001$, and $\eta^2 = 0.67$ (see Figure 4).

Simple contrasts revealed that the current mental state after the stress induction was significantly reduced compared to baseline, $F(1,38) = 62.21$, $p < 0.001$, and the exercise condition, $F(1,38) = 74.26$, $p < 0.001$. There was no significant interaction between group and condition, $F(2,76) = 1.47$, $p = 0.24$, and $\eta^2 = 0.04$.

Besides the self-report measure of mood, we also evaluated heart rate in the three different conditions. The lowest heart rate was found in the baseline condition (M = 73.04, SD = 14.01), followed by the stress (M = 85.90, SD = 17.53) and the exercise condition (M = 88.20, SD = 15.94). An ANOVA for repeated measure with the factors *Condition* and *Group* showed again a significant difference for the conditions for the heart rate values, $F(2,76) = 60.68$, $p < 0.001$, and $\eta^2 = 0.62$. Simple contrasts showed a significant difference in heart rate between baseline condition and both stress condition, $F(1,38) = 45.59$, $p < 0.001$, and exercise condition, $F(1,38) = 106.11$, $p < 0.001$, and a significant difference between the stress condition and the exercise condition, $F(1,38) = 6.53$, $p = 0.02$. There was no significant interaction of group x condition, $F(2,76) = 0.05$, $p = 0.96$, and $\eta^2 = 0.00$.

Using a repeated measures ANOVA on the HBP values with the factors *Condition* and *Group*, no main effect for

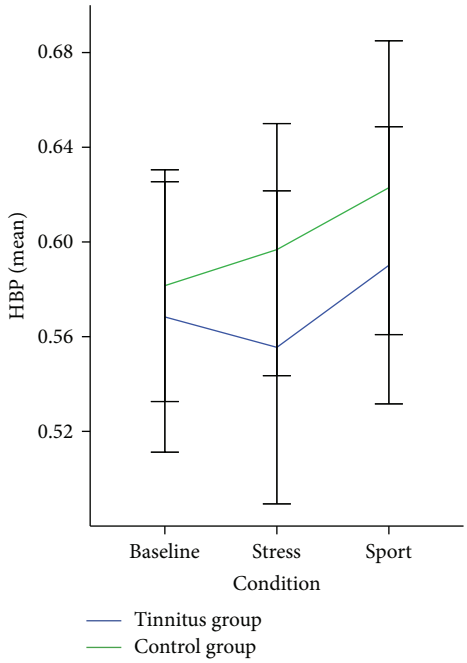


Figure 5: Heartbeat perception score (HBP) of the tinnitus and control group in the three conditions (baseline, stress, and exercise) of the Schandry task. Error bars indicate the standard error.

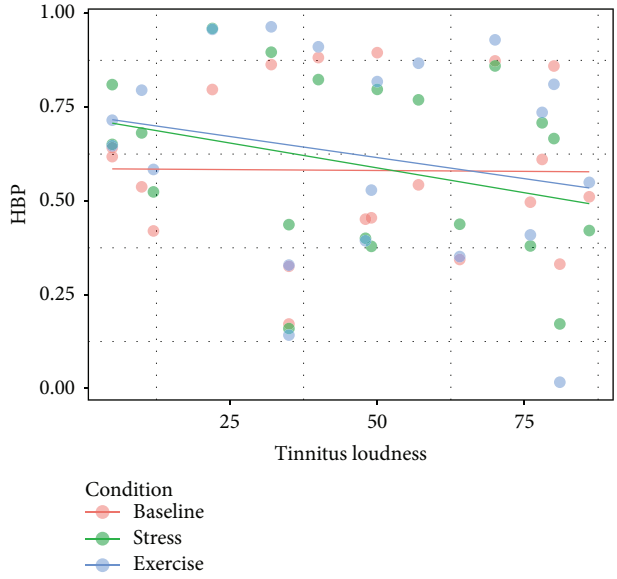


Figure 6: Correlation between the heart beat perception (HBP) score and tinnitus loudness. The correlation is plotted separately for the three conditions of the Schandry task. Colored lines represent the linear regression lines for each condition.

groups with regard to HBP, $F(2,76) = 1.90$, $p = 0.16$, nor an interaction effect, $F(2,76) = 0.30$, $p = 0.73$, was found (see Figure 5).

3.4. Post Hoc Analysis. An analysis of covariance (ANCOVA) for the performance in the Schandry task in the three conditions within the tinnitus group was conducted, using tinnitus loudness as a covariate. Bonferroni correction for multiple testing was applied. This analysis revealed a significant difference between the three conditions when controlling tinnitus loudness, $F(2,36) = 5.16$, $p = 0.02$, as well as the interaction condition x loudness, $F(2,36) = 4.39$, $p = 0.04$ (see Figure 6). A simple linear regression analysis to predict the performance in the Schandry task for the stress condition compared to the baseline condition revealed a significant influence of tinnitus loudness, $F(1,18) = 8.55$, $p < 0.01$, and $R^2 = 0.28$. A marginally significant effect was found for the influence of loudness on the performance in the exercise condition, $F(1,18) = 3.99$, $p = 0.06$, and $R^2 = 0.18$. Quiet tinnitus went along with an enhanced performance in the Schandry task, especially in the stress and exercise condition, whereas loud tinnitus is accompanied with a decreased performance in the stress and exercise task.

A second ANCOVA for repeated measures for the performance in the Schandry task with BMI as covariate did not reach significance level, $F(2,74) = 0.37$, $p > 0.99$ (again Bonferroni corrected for multiple comparisons).

4. Discussion

We evaluated whether interoceptive sensibility and accuracy as key factors of interoception differed in a sample with chronic tinnitus and healthy control subjects. We found no clinically relevant differences between the groups, neither using questionnaires (interoceptive sensibility) nor using experimental tasks (the Schandry task and a skin conductance task, interoceptive accuracy). However, a trend in the bias measure C towards a more liberal perception of arousal, that is, a higher preparedness to expect internal arousal, in the tinnitus group was detected. Furthermore, tinnitus loudness influenced performance on the Schandry task in the chronic tinnitus group.

In order to detect a clinically relevant influence of interoception on tinnitus, we based our *a priori* power calculations on the averaged effect size from a review [32] for the Schandry task, which is the most field-tested and standardized task for interoception. However, our results show that changes in interoception in chronic tinnitus are not comparable to anxiety disorders.

Our hypothesis that the tinnitus group might perform better in interoceptive accuracy when stressed, that is, trying to roughly simulate the cooccurrence of stress and tinnitus onset, was not supported by the obtained experimental results. Given the comparable heart frequency, we assumed that the origin of the heart beat differences, stress or exercise, might have an influence on interoception. Yet there was no difference between performance in the two conditions, nor an interaction effect between group and condition. Heart beat elevation and the self-report of mental state after the stress induction reflect a successful manipulation. Yet we do not know how long the elevated stress level after the induction lasted. At least before the beginning of the exercise condition, the stress levels went back to normal. It might be worth to enhance the stress level more persistently or "refresh" the stress level between each trial in order to come

to a final conclusion about the connection of stress level and interoceptive accuracy.

If we evaluate loudness of the tinnitus as a covariate for the Schandry task performance, we find a significant difference for the conditions in the Schandry task. The louder the tinnitus, the worse the heart beat perception performance in the stress and exercise condition. In the baseline condition, the cognitive load is lower and the cognitive resources are not yet depleted. Thus, it can be hypothesized that, with a quiet tinnitus perception, attention shifts are still possible as the participants were able to take away their attention from the tinnitus and focus on the task. If the tinnitus is especially loud, this might reduce the capacity to direct the attention away from the tinnitus towards perception of the heartbeat. This is in line with previous findings of difficulties of especially severe tinnitus sufferers on selective and divided attention [54, 55].

As the BMI negatively correlates with interoceptive accuracy for the heartbeat [56], the significant difference between the groups regarding this factor may have influenced the results as well. However, using BMI as covariate did not change our results.

The skin conductance task especially suffered from a low power: due to its novelty, effect sizes were difficult to estimate and in addition we encountered an unexpectedly significant number of dropouts. Furthermore, both groups had a low d' score, representing guessing probability in this task. Whereas this finding is not completely surprising, given that in the two previous studies d' scores in healthy control groups were also low, in our study the d' scores were lower than what was previously found [28, 30]. Obviously, the task was too difficult for both groups and the especially low d' scores render it unlikely that chronic tinnitus sufferers are especially adept at perceiving phasic sympathetic arousal as indexed by nonspecific skin conductance fluctuations.

Notwithstanding the bias C calculation is interesting. This finding adumbrates that the tinnitus group tends to perceive a bodily sensation, regardless of its actual physical occurrence. This perception bias might also apply to internal acoustic sensations and might be a starting point for a tinnitus sensation. Another possible explanation for the current results might be that people suffering from tinnitus may only have specifically increased interoception for internal acoustic processes which would not be detected through the measures used in the study at hand. Albeit we try to cover the concept of interoception as broad as possible, those measures might have been too coarse to detect this idea about specific and solely auditory interoception.

In contrast to these findings of interoceptive accuracy, another study found a reduced discrimination of external, electromagnetically evoked stimuli [57]. In the future, it might be interesting to investigate the relationship between extro- and interoception in tinnitus.

Overall our population was lowly distressed through their tinnitus. According to severity grading [58], 45% of our subjects had negligible tinnitus which is only audible in quiet surroundings, 40% a light tinnitus which can easily be ignored, and the rest mild tinnitus, where daily functioning is not impaired. The two more severe categories were not represented within our study. Through our screening for mental disorders, we might have likewise excluded highly distressed tinnitus sufferers as high distress in tinnitus is often accompanied by a mental disorder [59]. We would assume that in a high distressed group interoceptive processes might be more pronounced. This is also a key distinctive characteristic which varies between our study and the studies on interoception in mental disorders. In order to be diagnosed with a mental disorder, high distress and impairment are necessary; in the study at hand, we explicitly excluded participants based on this aspect.

Concluding, as first study in this field we tried to track down interoception in tinnitus. We took recent developments into consideration and systematically analyzed different aspects of interoception. In order to exclude confounders of interoception, we matched the two groups and profoundly screened for mental disorders. Despite our reasoning, we did not detect any main differences between a tinnitus group and a group of healthy controls regarding interoceptive accuracy and sensibility. If there are differences in the interoception between the two groups, the impact is not comparable to other disorders, for example, panic disorder and eating disorders. Yet we found that tinnitus sufferers might have a bias to perceive bodily symptoms irrespective of a physiological basis. Finally, we found that the loudness of tinnitus goes along with a decrease in performance in cognitive demanding tasks. We think it might be worth to further investigate the bias effect on the tinnitus population and to continue to complete the analysis of clinically relevant psychological variables influencing tinnitus and its distress.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

The authors are grateful to Gerhard Mutz, Karin Berning, and Louisa Hegermann for support in the measurements. This research was supported by DFG (PA 392/14-1) and Interdisziplinäres Zentrum für klinische Forschung (IZKF; CRA05).

References

[1] R. R. Coles, "Epidemiology of tinnitus: (1) prevalence," *The Journal of Laryngology & Otology*, vol. 98, supplement 9, pp. 7–15, 1984.

[2] R. A. Dobie, "Depression and tinnitus," *Otolaryngologic Clinics of North America*, vol. 36, no. 2, pp. 383–388, 2003.

[3] C. Pantev, H. Okamoto, and H. Teismann, "Tinnitus: the dark side of the auditory cortex plasticity," *Annals of the New York Academy of Sciences*, vol. 1252, no. 1, pp. 253–258, 2012.

[4] W. Schlee, N. Mueller, T. Hartmann, J. Keil, I. Lorenz, and N. Weisz, "Mapping cortical hubs in tinnitus," *BMC Biology*, vol. 7, article 80, 2009.

[5] G. Andersson and L. McKenna, "The role of cognition in tinnitus," *Acta Oto-Llaryngologica—Supplementum*, no. 556, pp. 39–43, 2006.

[6] D. De Ridder, S. Vanneste, N. Weisz et al., "An integrative model of auditory phantom perception: tinnitus as a unified percept of interacting separable subnetworks," *Neuroscience & Biobehavioral Reviews*, vol. 44, pp. 16–32, 2014.

[7] L. McKenna, L. Handscomb, D. J. Hoare, and D. A. Hall, "A scientific cognitive-behavioral model of tinnitus: novel conceptualizations of tinnitus distress," *Frontiers in Neurology*, vol. 5, article 196, 15 pages, 2014.

[8] D. M. Clark, "A cognitive approach to panic," *Behaviour Research and Therapy*, vol. 24, no. 4, pp. 461–470, 1986.

[9] S. Reiss and R. J. McNally, "The expectancy model of fear," in *Theoretical Issues in Behavior Therapy*, pp. 107–122, Academic Press, 1985.

[10] S. N. Garfinkel and H. D. Critchley, "Interoception, emotion and brain: new insights link internal physiology to social behaviour. Commentary on: 'anterior insular cortex mediates bodily sensibility and social anxiety' by Terasawa et al. (2012)," *Social Cognitive and Affective Neuroscience*, vol. 8, no. 3, pp. 231–234, 2013.

[11] M. Klabunde, D. T. Acheson, K. N. Boutelle, S. C. Matthews, and W. H. Kaye, "Interoceptive sensitivity deficits in women recovered from bulimia nervosa," *Eating Behaviors*, vol. 14, no. 4, pp. 488–492, 2013.

[12] O. Pollatos, A.-L. Kurz, J. Albrecht et al., "Reduced perception of bodily signals in anorexia nervosa," *Eating Behaviors*, vol. 9, no. 4, pp. 381–388, 2008.

[13] M. Schaefer, B. Egloff, and M. Witthöft, "Is interoceptive awareness really altered in somatoform disorders? Testing competing theories with two paradigms of heartbeat perception," *Journal of Abnormal Psychology*, vol. 121, no. 3, pp. 719–724, 2012.

[14] L. F. Barrett, K. S. Quigley, E. Bliss-Moreau, and K. R. Aronson, "Interoceptive sensitivity and self-reports of emotional experience," *Journal of Personality and Social Psychology*, vol. 87, no. 5, pp. 684–697, 2004.

[15] O. Pollatos and R. Schandry, "Emotional processing and emotional memory are modulated by interoceptive awareness," *Cognition and Emotion*, vol. 22, no. 2, pp. 272–287, 2008.

[16] B. M. Herbert, C. Herbert, and O. Pollatos, "On the relationship between interoceptive awareness and alexithymia: is interoceptive awareness related to emotional awareness?" *Journal of Personality*, vol. 79, no. 5, pp. 1149–1175, 2011.

[17] J. Salonen, R. Johansson, and M. Joukamaa, "Alexithymia, depression and tinnitus in elderly people," *General Hospital Psychiatry*, vol. 29, no. 5, pp. 431–435, 2007.

[18] M. R. Laureano, E. T. Onishi, R. A. Bressan et al., "Memory networks in tinnitus: a functional brain image study," *PLoS ONE*, vol. 9, no. 2, Article ID e87839, 2014.

[19] H.-U. W. T. Lang, S. Helbig-Lang, D. Westphal, and A. T. Gloster, *Expositionsbasierte Therapie der Panikstörung mit Agoraphobie: Ein Behandlungsmanual Broschiert*, 22nd edition, 2011.

[20] G. G. Birgit Kröner-Herwig and B. Jäger, *Tinnitus: Kognitiv-verhaltenstherapeutisches Behandlungsmanual. Mit Online-Materialien*, 2010.

[21] B. Kröner-Herwig, A. Frenzel, G. Fritsche, G. Schilkowsky, and G. Esser, "The management of chronic tinnitus: comparison of an outpatient cognitive-behavioral group training to minimal-contact interventions," *Journal of Psychosomatic Research*, vol. 54, no. 4, pp. 381–389, 2003.

[22] A. D. Craig, "Interoception: the sense of the physiological condition of the body," *Current Opinion in Neurobiology*, vol. 13, no. 4, pp. 500–505, 2003.

[23] H. D. Critchley, S. Wiens, P. Rotshtein, A. Öhman, and R. J. Dolan, "Neural systems supporting interoceptive awareness," *Nature Neuroscience*, vol. 7, no. 2, pp. 189–195, 2004.

[24] A. H. Lockwood, R. J. Salvi, M. L. Coad, M. L. Towsley, D. S. Wack, and B. W. Murphy, "The functional neuroanatomy of tinnitus: evidence for limbic system links and neural plasticity," *Neurology*, vol. 50, no. 1, pp. 114–120, 1998.

[25] S. Vanneste, M. Plazier, E. Van der Loo, M. Congedo, and D. De Ridder, "The neural correlates of tinnitus-related distress," *NeuroImage*, vol. 52, no. 2, pp. 470–480, 2010.

[26] E. van der Loo, M. Congedo, S. Vanneste, P. Van De Heyning, and D. De Ridder, "Insular lateralization in tinnitus distress," *Autonomic Neuroscience: Basic and Clinical*, vol. 165, no. 2, pp. 191–194, 2011.

[27] S. N. Garfinkel, A. K. Seth, A. B. Barrett, K. Suzuki, and H. D. Critchley, "Knowing your own heart: distinguishing interoceptive accuracy from interoceptive awareness," *Biological Psychology*, vol. 104, pp. 65–74, 2015.

[28] S. Krautwurst, A. L. Gerlach, L. Gomille, W. Hiller, and M. Witthöft, "Health anxiety—an indicator of higher interoceptive sensitivity?" *Journal of Behavior Therapy and Experimental Psychiatry*, vol. 45, no. 2, pp. 303–309, 2014.

[29] R. Schandry, "Heart beat perception and emotional experience," *Psychophysiology*, vol. 18, no. 4, pp. 483–488, 1981.

[30] T. Andor, A. L. Gerlach, and F. Rist, "Superior perception of phasic physiological arousal and the detrimental consequences of the conviction to be aroused on worrying and metacognitions in GAD," *Journal of Abnormal Psychology*, vol. 117, no. 1, pp. 193–205, 2008.

[31] A. Katzer, D. Oberfeld, W. Hiller, A. L. Gerlach, and M. Witthöft, "Tactile perceptual processes and their relationship to somatoform disorders," *Journal of Abnormal Psychology*, vol. 121, no. 2, pp. 530–543, 2012.

[32] K. Domschke, S. Stevens, B. Pfleiderer, and A. L. Gerlach, "Interoceptive sensitivity in anxiety and anxiety disorders: an overview and integration of neurobiological findings," *Clinical Psychology Review*, vol. 30, no. 1, pp. 1–11, 2010.

[33] B. Mazurek, T. Stöver, H. Haupt et al., "The significance of stress: its role in the auditory system and the pathogenesis of tinnitus," *HNO*, vol. 58, no. 2, pp. 162–172, 2010.

[34] A. Baigi, A. Oden, V. Almlid-Larsen, M.-L. Barrenäs, and K.-M. Holgers, "Tinnitus in the general population with a focus on noise and stress: a public health study," *Ear and Hearing*, vol. 32, no. 6, pp. 787–789, 2011.

[35] S. Hébert and S. J. Lupien, "The sound of stress: blunted cortisol reactivity to psychosocial stress in tinnitus sufferers," *Neuroscience Letters*, vol. 411, no. 2, pp. 138–142, 2007.

[36] M. Wittchen, H.-U. Wunderlich, U. Gruschwitz, and S. Zaudig, *SKID I—Strukturiertes Klinisches Interview für DSM-IV—Achse—I: Psychische Störungen*, Hogrefe, Göttingen, Germany, 1997.

[37] W. E. Mehling, V. Gopisetty, J. Daubenmier, C. J. Price, F. M. Hecht, and A. Stewart, "Body awareness: construct and self-report measures," *PLoS ONE*, vol. 4, no. 5, Article ID e5614, 2009.

[38] S. A. Shields, M. E. Mallory, and A. Simon, "The body awareness questionnaire: reliability and validity," *Journal of Personality Assessment*, vol. 53, no. 4, pp. 802–815, 1989.

[39] L. C. Miller, R. Murphy, and A. H. Buss, "Consciousness of body: private and public," *Journal of Personality and Social Psychology*, vol. 41, no. 2, pp. 397–406, 1981.

[40] W. E. Mehling, C. Price, J. J. Daubenmier, M. Acree, E. Bartmess, and A. Stewart, "The multidimensional assessment of interoceptive awareness (MAIA)," *PLoS ONE*, vol. 7, no. 11, Article ID e48230, 2012.

[41] A. J. Christensen, J. S. Wiebe, D. L. Edwards, J. D. Michels, and W. J. Lawton, "Body consciousness, illness-related impairment, and patient adherence in hemodialysis," *Journal of Consulting and Clinical Psychology*, vol. 64, no. 1, pp. 147–152, 1996.

[42] B. Bornemann, B. M. Herbert, W. E. Mehling, and T. Singer, "Differential changes in self-reported aspects of interoceptive awareness through 3 months of contemplative training," *Frontiers in Psychology*, vol. 5, article 1504, 13 pages, 2015.

[43] D. Watson, L. A. Clark, and A. Tellegen, "Development and validation of brief measures of positive and negative affect: the PANAS scales," *Journal of Personality and Social Psychology*, vol. 54, no. 6, pp. 1063–1070, 1988.

[44] J. Rief, W. Hiller, and W. Heuser, *SOMS, das Screening für somatoforme Störungen: Manual zum Fragebogen [SOMS, Screening for Somatoform Disorders: The Questionnaire Manual]*, Hubors, Bern, Switzerland, 1997.

[45] F. K. Kuk, R. S. Tyler, D. Russell, and H. Jordan, "The psychometric properties of a tinnitus handicap questionnaire," *Ear and Hearing*, vol. 11, no. 6, pp. 434–445, 1990.

[46] C. W. Newman, G. P. Jacobson, and J. B. Spitzer, "Development of the tinnitus handicap inventory," *Archives of Otolaryngology—Head and Neck Surgery*, vol. 122, no. 2, pp. 143–148, 1996.

[47] D. C. Fowles, M. J. Christie, R. Edelberg, W. W. Grings, D. T. Lykken, and P. H. Venables, "Committee report. Publication recommendations for electrodermal measurements," *Psychophysiology*, vol. 18, pp. 232–239, 1981.

[48] W. Boucsein, *Elektrodermale Aktivität: Grundlagen. Methoden und Anwendungen*, Springer, Berlin, Germany, 1988.

[49] R. Steyer, P. Schwenkmezger, and P. Notz, *Der Mehrdimensionale Befindlichkeitsfragebogen (MDBF)*, vol. 31, Hogrefe, 1997.

[50] L. Elling, H. Schupp, J. Bayer et al., "The impact of acute psychosocial stress on magnetoencephalographic correlates of emotional attention and exogenous visual attention," *PLoS ONE*, vol. 7, no. 6, Article ID e35767, 2012.

[51] C. Kirschbaum, K.-M. Pirke, and D. H. Hellhammer, "The 'trier social stress test'—a tool for investigating psychobiological stress responses in a laboratory setting," *Neuropsychobiology*, vol. 28, no. 1-2, pp. 76–81, 1993.

[52] O. Pollatos, W. Kirsch, and R. Schandry, "On the relationship between interoceptive awareness, emotional experience, and brain processes," *Cognitive Brain Research*, vol. 25, no. 3, pp. 948–962, 2005.

[53] C. Ring and J. Brener, "Influence of beliefs about heart rate and actual heart rate on heartbeat counting," *Psychophysiology*, vol. 33, no. 5, pp. 541–546, 1996.

[54] C. Stevens, G. Walker, M. Boyer, and M. Gallagher, "Severe tinnitus and its effect on selective and divided attention," *International Journal of Audiology*, vol. 46, no. 5, pp. 208–216, 2007.

[55] S. Rossiter, C. Stevens, and G. Walker, "Tinnitus and its effect on working memory and attention," *Journal of Speech, Language, and Hearing Research*, vol. 49, no. 1, pp. 150–160, 2006.

[56] B. M. Herbert, J. Blechert, M. Hautzinger, E. Matthias, and C. Herbert, "Intuitive eating is associated with interoceptive sensitivity. Effects on body mass index," *Appetite*, vol. 70, pp. 22–30, 2013.

[57] M. Landgrebe, U. Frick, S. Hauser, G. Hajak, and B. Langguth, "Association of tinnitus and electromagnetic hypersensitivity: hints for a shared pathophysiology?" *PLoS ONE*, vol. 4, no. 3, Article ID e5026, 2009.

[58] A. McCombe, D. Baguley, R. Coles, L. McKenna, C. McKinney, and P. Windle-Taylor, "Guidelines for the grading of tinnitus severity: the results of a working group commissioned by the British Association of Otolaryngologists, Head and Neck Surgeons, 1999," *Clinical Otolaryngology and Allied Sciences*, vol. 26, no. 5, pp. 388–393, 2001.

[59] N. Zirke, G. Goebel, and B. Mazurek, "Tinnitus and psychological comorbidities," *HNO*, vol. 58, no. 7, pp. 726–732, 2010.

Hindawi Publishing Corporation
BioMed Research International
Volume 2015, Article ID 461090, 6 pages
http://dx.doi.org/10.1155/2015/461090

Research Article

Psychophysiological Associations between Chronic Tinnitus and Sleep: A Cross Validation of Tinnitus and Insomnia Questionnaires

Martin Schecklmann,[1] Maximilian Pregler,[1] Peter M. Kreuzer,[1] Timm B. Poeppl,[1] Astrid Lehner,[1] Tatjana Crönlein,[1] Thomas C. Wetter,[1] Elmar Frank,[1] Michael Landgrebe,[2] and Berthold Langguth[1]

[1]*Department of Psychiatry and Psychotherapy, University of Regensburg, 93055 Regensburg, Germany*
[2]*Department of Psychiatry, Psychosomatics and Psychotherapy, kbo-Lech-Mangfall-Klinik Agatharied, 83734 Hausham, Germany*

Correspondence should be addressed to Martin Schecklmann; martin.schecklmann@medbo.de

Received 1 March 2015; Accepted 25 April 2015

Academic Editor: Aage R. Møller

Background. The aim of the present study was to assess the prevalence of insomnia in chronic tinnitus and the association of tinnitus distress and sleep disturbance. *Methods*. We retrospectively analysed data of 182 patients with chronic tinnitus who completed the Tinnitus Questionnaire (TQ) and the Regensburg Insomnia Scale (RIS). Descriptive comparisons with the validation sample of the RIS including exclusively patients with primary/psychophysiological insomnia, correlation analyses of the RIS with TQ scales, and principal component analyses (PCA) in the tinnitus sample were performed. TQ total score was corrected for the TQ sleep items. *Results*. Prevalence of insomnia was high in tinnitus patients (76%) and tinnitus distress correlated with sleep disturbance ($r = 0.558$). TQ sleep subscore correlated with the RIS sum score ($r = 0.690$). PCA with all TQ and RIS items showed one sleep factor consisting of all RIS and the TQ sleep items. PCA with only TQ sleep and RIS items showed sleep- and tinnitus-specific factors. The sleep factors (only RIS items) were sleep depth and fearful focusing. The TQ sleep items represented tinnitus-related sleep problems. *Discussion*. Chronic tinnitus and primary insomnia are highly related and might share similar psychological and neurophysiological mechanisms leading to impaired sleep quality.

1. Introduction

Several neural models regarding the generation and maintenance of chronic and bothersome tinnitus postulate that cochlear dysfunction may be associated with adaptive processes involving both auditory pathway and nonauditory areas (for overview [1]). Patients report difficulties distracting themselves from their tinnitus or negatively appraise their tinnitus, which is in line with the notion of attention (frontoparietal areas) and distress (limbic areas) network involvement in chronic tinnitus [2]. Moreover, increased connectivity between auditory and emotional/autonomic areas has been described in tinnitus patients [3]. An early neurophysiological model suggests that negative emotional and cognitive reaction to the tinnitus percept leads to a distress response of the autonomic nervous system [4, 5]. By mechanisms of conditioned reflexes the tinnitus percept is reinforced by the negative autonomic reaction. These interactions between auditory and nonauditory brain regions can explain why tinnitus is perceived as bothersome and might be the reason why habituation to the tinnitus percept is prevented. These mechanisms can lead to comorbid conditions such as concentration problems, depressivity, and sleep disturbances [6]. Accordingly, insomnia shows an increased prevalence in chronic tinnitus [7, 8] and an impaired sleep quality is correlated with tinnitus distress and sleep quality [9]. Patients frequently report that tinnitus prevents them from falling asleep. Moreover, tinnitus perception and annoyance depends on the quality of the night's sleep and also of afternoon naps. Patients with chronic tinnitus show altered

sleep architecture with a higher amount of light sleep as compared to healthy controls [10]. Another study comparing patients with chronic tinnitus and healthy controls showed no differences in polysomnographic sleep parameters except lower nonrapid eye movement spectral power in delta band which was correlated with subjective sleep complaints [11] and lower subjective sleep quality in tinnitus. Insomnia patients with and without tinnitus revealed similar impaired sleep architecture [12]. First trials with sleep-regulating medication such as melatonin showed divergent results [13, 14].

Recently, dysfunctional cognitions, hyperarousal, and increased sympathetic activation were discussed as common etiological factors in comorbid tinnitus and sleep disorders [15]. Primary or psychophysiological insomnia—insomnia without comorbid somatic or psychiatric disorders—is characterised by a physiological hyperarousal, impaired sleep quality, associated tiredness, dysfunctional thinking about sleep, and unfavourable sleeping habits [16]. Recently, parts of the cingulate cortex and bilateral insula were identified as neural substrate for abnormal autonomous activity as elicited by heart rate variability, which in turn is mediating tinnitus distress [17].

Based on the idea of common etiological factors in chronic tinnitus and psychophysiological insomnia [15], the aim of the present study was to assess the prevalence of insomnia in chronic tinnitus and the association of tinnitus distress and sleep disturbance. Furthermore, we evaluated whether the Tinnitus Questionnaire (TQ [18]) is sufficient for screening of insomnia symptoms in chronic tinnitus. For this purpose a retrospective analysis of the association of the TQ and the Regensburg Insomnia Scale (RIS [12]) of a large sample of patients with chronic tinnitus was performed. The TQ is a validated questionnaire for the assessment of tinnitus severity with a well-established factorial structure. Among the 6 components one factor assesses specifically sleep problems. The RIS was specifically established for the assessment of psychological factors related to primary/psychophysiological insomnia [19].

2. Materials and Methods

All included subjects were patients of the in- or outpatient clinic of the Department of Psychiatry and Psychotherapy. Tinnitus was diagnosed in the outpatient clinic which is part of the Interdisciplinary Tinnitus Center at the University of Regensburg (Regensburg, Germany). Patients gave written informed consent for data collection in the Tinnitus Research Initiative database [20] which was approved by the Ethics Committee of the University Hospital of Regensburg (Germany; reference number 08/046). Inclusion criterion was subjective chronic tinnitus. Exclusion criteria were objective tinnitus (with a treatable cause) and presence of unstable psychiatric comorbidities or unstable medical conditions. Patients were 53 ± 11.1 years old; 129 out of 182 (71%) were men, and had a tinnitus duration of 98.2 ± 99.2 ($n = 171$) months and tinnitus distress level of 46.3 ± 18.0 as indicated by the TQ. Seventeen out of 177 showed purely right, 32 purely left tinnitus and 128 tinnitus in both ears or within the head.

Patients filled in the German versions of the Tinnitus Questionnaire (TQ [18, 21]) and the Regensburg Insomnia Scale (RIS [19]). The TQ total score is the summation of 40 items with 2 items counted double. The different subscales are emotional distress, cognitive distress, sleep disturbance, auditory perceptual difficulties, somatic complaints, and intrusiveness. To control for effects of sleep items in the TQ total score we subtracted the sleep subscore from TQ total score for the statistical analyses.

For statistical analysis we present descriptive comparisons of the present tinnitus sample with the insomnia sample of the validation study of the RIS [19]. The validation sample was recruited and carefully diagnosed in the Center for Sleep Medicine at the Department of Psychiatry and Psychotherapy of the University of Regensburg (Germany). We correlated the RIS sum score with the TQ scales using Pearson correlation coefficient. Contrasts between correlations were done by using Fisher's r-to-z transformation. Two principal component analyses (PCAs) with Varimax rotation were used to test for the homogeneity of the TQ sleep and the RIS items. For the first PCA all TQ items and all RIS items were included; for the second PCA only TQ sleep items and the RIS items were included. To test for the homogeneity between tinnitus and insomnia patients we recalculated the PCA of the RIS validation study for the present tinnitus sample by using only the RIS items. For factor extraction we used the Kaiser-Guttman criterion (eigenvalues > 1). According to Hair et al. [22] items with factor loadings above 0.45 were included for the factor solution. Statistical analyses were performed with SPSS 18.0.0 (SPSS, USA).

3. Results

138 out of 182 tinnitus patients (76%) presented with insomnia as categorised by the cut-off score of the RIS (>12). The mean RIS score (17.5 ± 7.6) was about five points below the mean RIS score of the validation sample [22] which included only patients with primary insomnia. On single item level the difference between the two samples was in the same range except for the items nine and ten. With respect to those two items ("*daytime functioning*" and "*medication intake*") tinnitus and insomnia patients had similar values (Table 1).

Tinnitus patients showed significant medium to high correlations of the RIS sum score with the total score of the TQ (corrected for the sleep items) and all subscores (Table 2). The correlation of the RIS with the sleep subscore was the highest one. The correlation between the RIS and the TQ sleep subscore was significantly higher than the correlation of the RIS with the other TQ scores (Table 2).

Principal component analyses with all TQ and RIS items fulfilled the statistical requirements (Kaiser-Meyer-Olkin measure: KMO = 0.905; Bartlett's test: $p < 0.001$) and showed ten factors including one sleep factor consisting of three of the TQ sleep items and the RIS items 2–8 (Table 3). Principal component analyses with all sleep items (four TQ sleep items and all RIS items) fulfilled the statistical requirements (Kaiser-Meyer-Olkin measure: KMO = 0.900; Bartlett's test: $p < 0.001$) and showed three factors. Factor one consisted

Table 1: Characterization of the sleep items of the Regensburg Insomnia Scale and the Tinnitus Questionnaire sleep subscore items and comparison of the mean scores of the present tinnitus sample with the validation sample of the Regensburg Insomnia Scale.

Items		Insomnia sample $n = 218$	Tinnitus sample $n = 182$	Difference score
	Regensburg Insomnia Scale			
1	Sleep onset latency	1.82 ± 1.37	1.21 ± 1.13	0.61
2	Sleep duration	1.65 ± 0.86	1.02 ± 0.88	0.63
3	Disturbed sleep	3.11 ± 0.97	2.27 ± 1.2	0.84
4	Early awakening	2.86 ± 1.03	2.25 ± 1.09	0.61
5	Awaking by sounds	2.77 ± 1.08	2.25 ± 1.07	0.52
6	Feeling of no night sleep	2.07 ± 0.97	1.53 ± 1.04	0.54
7	Thinking about sleep	2.41 ± 0.92	1.79 ± 1.08	0.62
8	Afraid of going to bed	1.89 ± 1.24	1.48 ± 1.25	0.41
9	Daytime functioning	2.31 ± 1.03	2.12 ± 1.09	0.19
10	Medication intake	1.7 ± 1.56	1.52 ± 1.67	0.18
	Tinnitus Questionnaire			
4	Awakening more often due to tinnitus			
12	Early awakening due to tinnitus			
31	Sleep as general problem			
36	Sleep onset latency due to tinnitus			

Table 2: Correlation analyses between RIS (Regensburg Insomnia Scale) sum score and TQ (Tinnitus Questionnaire) scores. Please note that TQ total score is corrected for the sleep subscore.

	RIS sum score	Correlation differences of TQ-RIS with RIS-TQ sleep score
TQ score sleep disturbance	$r = 0.690$; $p < 0.001$	—
TQ total score	$r = 0.558$; $p < 0.001$	$z = 2.06$; $p = 0.039$
TQ score cognitive distress	$r = 0.545$; $p < 0.001$	$z = 2.24$; $p = 0.025$
TQ score emotional distress	$r = 0.452$; $p < 0.001$	$z = 3.41$; $p < 0.001$
TQ score intrusiveness	$r = 0.450$; $p < 0.001$	$z = 3.44$; $p < 0.001$
TQ score auditory perceptual difficulties	$r = 0.371$; $p < 0.001$	$z = 4.34$; $p < 0.001$
TQ score somatic complaints	$r = 0.462$; $p < 0.001$	$z = 3.21$; $p = 0.001$

of the RIS items 2–6 (sleep depth), factor two consisted of all TQ sleep items (tinnitus-related sleep), and factor three consisted of RIS items 1, 7, and 8 (fearful focusing and sleep onset). Principal component analyses with only the RIS items fulfilled the statistical requirements (Kaiser-Meyer-Olkin measure: KMO = 0.871; Bartlett's test: $p < 0.001$) and showed two factors. Factor one consisted of the RIS items 2–6 (*sleep depth*) and factor two consisted of items 7 and 8 (*fearful focusing*). The factors *fearful focusing* and *sleep depth* were also extracted in the insomnia validation sample whereas the other extracted factors from the validation sample (*sleep quantity* and *sleep medication/daytime functioning*) could not be extracted in our sample.

4. Discussion

Our retrospective correlation analysis of Tinnitus Questionnaire (TQ) and Regensburg Insomnia Scale (RIS) in 182 patients with chronic tinnitus showed three main results.

(1) According to the cut-off of the RIS sum score 76% of all tinnitus patients in our sample suffer from insomnia. This finding emphasizes that insomnia represents a major problem in chronic tinnitus. With respect to daytime functioning and sleep medication intake tinnitus patients display similar scores as patients with primary insomnia. The correlation analyses revealed a rather high association ($r = 0.558$) between tinnitus distress (TQ sum score corrected for the sleep items) and sleep disturbance (RIS score). This finding is in line with recent results of a significant correlation of 0.62 in 117 US tinnitus patients between the Tinnitus Reaction Questionnaire and the Insomnia Severity Index [23]. In another study of 97 veterans with tinnitus a small association of 0.214 between the Tinnitus Handicap Inventory (measuring tinnitus distress) and the Epworth Sleepiness Scale (measuring daytime sleepiness) was found [9]. Taken together these findings confirm consistently that sleep problems have an impact on tinnitus severity, but they also show that the exact magnitude of the relationship depends on sample selection and assessment instruments.

(2) The TQ sleep subscore is highly correlated with the RIS. Tinnitus-related sleep disturbance as indicated

Table 3: Factor solutions for the sleep components using principal component analyses (PCAs).

	PCA with all TQ and RIS items	PCA with only TQ sleep and RIS items			PCA with only RIS items	
	Factor 1	Factor 1	Factor 2	Factor 3	Factor 1	Factor 2
	Sleep	Sleep depth	Tinnitus-related sleep	Fearful focusing and sleep onset	Sleep depth	Fearful focusing
RIS items						
1	(0.357)			0.570		(0.434)
2	0.693	0.491			0.667	
3	0.705	0.686			0.799	
4	0.688	0.604			0.610	
5	0.628	0.556			0.553	
6	0.696	0.666			0.595	
7	0.606			0.507		0.638
8	0.542			0.531		0.774
9						
10						
TQ items						
4	0.531		0.768			
12	0.538		0.771			
31	0.582		0.537			
36	(0.389)		0.594			

Values in brackets lie below the a priori defined factor loading threshold of 0.45.

by the TQ explains about 48% ($r = 0.690$) of the variance of psychophysiological sleeping problems as indicated by the RIS which was constructed for measuring psychological aspects of insomnia. The PCA with all items of the TQ and RIS resulted in a common factor "*sleep*" including all RIS items and all four sleep items of the TQ. Thus, the TQ with its subscore structure seems to be sufficient as a screening tool for tinnitus-related insomnia. However, more detailed insights into the association between sleep and tinnitus are necessary for a more effective clinical management of tinnitus patients with insomnia. It remains unclear if the vicious circles of insomnia and tinnitus are connected by common symptoms such as dysfunctional beliefs or hyperarousal. It is also an open question if daytime tinnitus annoyance is dependent on sleep quality, sleep quantity, afternoon nap, or kind of sleep stage during awakening. Whereas clinical experience suggests such relationships, specific studies addressing these questions are still lacking. There is evidence that sleep deprivation, selective sleep interruption, and awakening in different sleep stages exert influences on experimentally induced pain [24, 25]. In light of the overlap in neurophysiological mechanisms of chronic pain and tinnitus [26], similar mechanisms could also hold for tinnitus.

(3) Based on the PCAs using only sleep items it turned out that fearful focusing and lack of sleep depth are the two main sleep-related problems in chronic tinnitus. Thus, tinnitus patients and those suffering from psychophysiological insomnia share similar sleep-related problems. In our clinical experience dysfunctional beliefs, negative thoughts, and hyperarousal are encountered in patients with both primary insomnia and chronic tinnitus. However, in tinnitus patients the focus of negative thoughts and emotions is related to both tinnitus and sleep and not to sleep alone. This may be the reason for subjectively experienced longer sleep onset latencies in tinnitus patients with insomnia in contrast to insomnia patients alone [12]. From a clinical perspective, it is to be tested if cognitive behavioural therapy for primary insomnia [27] could also be effective in chronic tinnitus with insomnia [28].

The big limitation of this study might be based on sample bias. As our sample derives from a tertiary referral center and our tinnitus center is known supraregionally, the sample is probably not representative and is rather limited to high-burdened patients although the mean tinnitus distress level was medium.

5. Conclusions

From a methodological point of view, our results suggest that the TQ sleep subscore is a good approximation of general sleep-related problems in tinnitus. However, more detailed information can be obtained by using specific questionnaires such as the RIS. Taking into account the specific single items of both examined questionnaires, psychological and physiological mechanisms seem to be similar in chronic tinnitus and primary insomnia. We suggest that future studies

should focus on the underlying neurobiological mechanisms of disturbed sleep in tinnitus and also of sleep-mediated tinnitus annoyance.

Conflict of Interests

None of the authors has any conflict of interests to disclose.

Authors' Contribution

Michael Landgrebe, Tatjana Crönlein, and Berthold Langguth designed the study. Martin Schecklmann, Michael Landgrebe, Elmar Frank, Peter M. Kreuzer, Timm B. Poeppl, Astrid Lehner, and Berthold Langguth conducted the study, including patient recruitment and data collection. Martin Schecklmann and Maximilian Pregler were responsible for the data analysis. Martin Schecklmann prepared the paper draft with important intellectual input from Tatjana Crönlein, Thomas C. Wetter, and Berthold Langguth. All authors approved the final paper.

Acknowledgments

The authors wish to thank Sandra Pfluegl, Ulrike Stadler, and Helene Niebling for technical assistance.

References

[1] P. Adjamian, D. A. Hall, A. R. Palmer, T. W. Allan, and D. R. Langers, "Neuroanatomical abnormalities in chronic tinnitus in the human brain," *Neuroscience & Biobehavioral Reviews*, vol. 45, pp. 119–133, 2014.

[2] D. De Ridder, S. Vanneste, N. Weisz et al., "An integrative model of auditory phantom perception: tinnitus as a unified percept of interacting separable subnetworks," *Neuroscience and Biobehavioral Reviews*, vol. 44, pp. 16–32, 2013.

[3] W. Schlee, N. Weisz, O. Bertrand, T. Hartmann, and T. Elbert, "Using auditory steady state responses to outline the functional connectivity in the tinnitus brain," *PLoS ONE*, vol. 3, no. 11, Article ID e3720, 2008.

[4] P. J. Jastreboff, "Phantom auditory perception (tinnitus): mechanisms of generation and perception," *Neuroscience Research*, vol. 8, no. 4, pp. 221–254, 1990.

[5] P. J. Jastreboff and J. W. P. Hazell, "A neurophysiological approach to tinnitus: clinical implications," *British Journal of Audiology*, vol. 27, no. 1, pp. 7–17, 1993.

[6] B. Langguth, "A review of tinnitus symptoms beyond 'ringing in the ears': a call to action," *Current Medical Research and Opinion*, vol. 27, no. 8, pp. 1635–1643, 2011.

[7] K. Izuhara, K. Wada, K. Nakamura et al., "Association between tinnitus and sleep disorders in the general Japanese population," *Annals of Otology, Rhinology & Laryngology*, vol. 122, no. 11, pp. 701–706, 2013.

[8] A. Fioretti, M. Fusetti, and A. Eibenstein, "Association between sleep disorders, hyperacusis and tinnitus: evaluation with tinnitus questionnaires," *Noise and Health*, vol. 15, no. 63, pp. 91–95, 2013.

[9] Y. F. Liu, J. Hu, M. Streelman, and O. W. Guthrie, "The epworth sleepiness scale in the assessment of sleep disturbance in veterans with tinnitus," *International Journal of Otolaryngology*, vol. 2015, Article ID 429469, 9 pages, 2015.

[10] G. Attanasio, F. Y. Russo, R. Roukos, E. Covelli, G. Cartocci, and M. Saponara, "Sleep architecture variation in chronic tinnitus patients," *Ear and Hearing*, vol. 34, no. 4, pp. 503–507, 2013.

[11] S. Hébert, S. Fullum, and J. Carrier, "Polysomnographic and quantitative electroencephalographic correlates of subjective sleep complaints in chronic tinnitus," *Journal of Sleep Research*, vol. 20, no. 1, pp. 38–44, 2011.

[12] T. Crönlein, B. Langguth, P. Geisler, and G. Hajak, "Tinnitus and insomnia," *Progress in Brain Research*, vol. 166, pp. 227–233, 2007.

[13] A. Hurtuk, C. Dome, C. H. Holloman et al., "Melatonin: can it stop the ringing?" *Annals of Otology, Rhinology & Laryngology*, vol. 120, no. 7, pp. 433–440, 2011.

[14] M. Miroddi, R. Bruno, F. Galletti et al., "Clinical pharmacology of melatonin in the treatment of tinnitus: a review," *European Journal of Clinical Pharmacology*, vol. 71, no. 3, pp. 263–270, 2015.

[15] E. Wallhäusser-Franke, M. Schredl, and W. Delb, "Tinnitus and insomnia: is hyperarousal the common denominator?" *Sleep Medicine Reviews*, vol. 17, no. 1, pp. 65–74, 2013.

[16] A. G. Harvey, "A cognitive model of insomnia," *Behaviour Research and Therapy*, vol. 40, no. 8, pp. 869–893, 2002.

[17] S. Vanneste and D. de Ridder, "Brain areas controlling heart rate variability in tinnitus and tinnitus-related distress," *PLoS ONE*, vol. 8, no. 3, Article ID e59728, 2013.

[18] G. Goebel and W. Hiller, "The tinnitus questionnaire. A standard instrument for grading the degree of tinnitus. Results of a multicenter study with the tinnitus questionnaire," *HNO*, vol. 42, no. 3, pp. 166–172, 1994.

[19] T. Crönlein, B. Langguth, R. Popp et al., "Regensburg Insomnia Scale (RIS): a new short rating scale for the assessment of psychological symptoms and sleep in insomnia; study design: development and validation of a new short self-rating scale in a sample of 218 patients suffering from insomnia and 94 healthy controls," *Health and Quality of Life Outcomes*, vol. 11, article 65, 2013.

[20] M. Landgrebe, F. Zeman, M. Koller et al., "The Tinnitus Research Initiative (TRI) database: a new approach for delineation of tinnitus subtypes and generation of predictors for treatment outcome," *BMC Medical Informatics and Decision Making*, vol. 10, no. 1, article 42, 2010.

[21] R. S. Hallam, S. C. Jakes, and R. Hinchcliffe, "Cognitive variables in tinnitus annoyance," *British Journal of Clinical Psychology*, vol. 27, no. 3, pp. 213–222, 1988.

[22] J. F. Hair, R. L. Tatham, R. E. Anderson, and W. Black, *Multivariate Data Analysis*, Prentice-Hall, London, UK, 1998.

[23] G. S. Miguel, K. Yaremchuk, T. Roth, and E. Peterson, "The effect of insomnia on tinnitus," *Annals of Otology, Rhinology & Laryngology*, vol. 123, pp. 696–700, 2014.

[24] S. H. Onen, A. Alloui, A. Gross, A. Eschallier, and C. Dubray, "The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subjects," *Journal of Sleep Research*, vol. 10, no. 1, pp. 35–42, 2001.

[25] V. G. Daya and A. J. Bentley, "Perception of experimental pain is reduced after provoked waking from rapid eye movement sleep," *Journal of Sleep Research*, vol. 19, no. 2, pp. 317–322, 2010.

[26] D. de Ridder, A. B. Elgoyhen, R. Romo, and B. Langguth, "Phantom percepts: tinnitus and pain as persisting aversive memory networks," *Proceedings of the National Academy of*

Sciences of the United States of America, vol. 108, no. 20, pp. 8075–8080, 2011.

[27] T. Crönlein, B. Langguth, P. Geisler, T. C. Wetter, and P. Eichhammer, "Fourteen-day inpatient cognitive-behavioural therapy for insomnia: a logical and useful extension of the stepped-care approach for the treatment of insomnia," *Psychotherapy and Psychosomatics*, vol. 83, no. 4, pp. 255–256, 2014.

[28] T. Cronlein, B. Langguth, S. Tauber et al., "Ein neues standardisiertes Kurzzeitprogramm zur Behandlung von Schlafstörungen bei Tinnituspatienten," *Psychiatrische Forschung*, vol. 1, no. 1, 2011.

Hindawi Publishing Corporation
BioMed Research International
Volume 2015, Article ID 302515, 5 pages
http://dx.doi.org/10.1155/2015/302515

Research Article

The Relevance of the High Frequency Audiometry in Tinnitus Patients with Normal Hearing in Conventional Pure-Tone Audiometry

Veronika Vielsmeier,[1] Astrid Lehner,[2] Jürgen Strutz,[1] Thomas Steffens,[1] Peter M. Kreuzer,[2] Martin Schecklmann,[2] Michael Landgrebe,[2,3] Berthold Langguth,[2] and Tobias Kleinjung[1,4]

[1]*Department of Otorhinolaryngology, University of Regensburg, 93053 Regensburg, Germany*
[2]*Department of Psychiatry and Psychotherapy, University of Regensburg, 93053 Regensburg, Germany*
[3]*Clinic Lech-Mangfall, 83734 Agatharied, Germany*
[4]*Department of Otorhinolaryngology, University of Zurich, 8091 Zürich, Switzerland*

Correspondence should be addressed to Veronika Vielsmeier; veronika.vielsmeier@ukr.de

Received 3 November 2014; Accepted 8 January 2015

Academic Editor: Claus-Peter Richter

Objective. The majority of tinnitus patients suffer from hearing loss. But a subgroup of tinnitus patients show normal hearing thresholds in the conventional pure-tone audiometry (125 Hz–8 kHz). Here we explored whether the results of the high frequency audiometry (>8 kHz) provide relevant additional information in tinnitus patients with normal conventional audiometry by comparing those with normal and pathological high frequency audiometry with respect to their demographic and clinical characteristics. *Subjects and Methods*. From the database of the Tinnitus Clinic at Regensburg we identified 75 patients with normal hearing thresholds in the conventional pure-tone audiometry. We contrasted these patients with normal and pathological high-frequency audiogram and compared them with respect to gender, age, tinnitus severity, pitch, laterality and duration, comorbid symptoms and triggers for tinnitus onset. *Results*. Patients with pathological high frequency audiometry were significantly older and had higher scores on the tinnitus questionnaires in comparison to patients with normal high frequency audiometry. Furthermore, there was an association of high frequency audiometry with the laterality of tinnitus. *Conclusion*. In tinnitus patients with normal pure-tone audiometry the high frequency audiometry provides useful additional information. The association between tinnitus laterality and asymmetry of the high frequency audiometry suggests a potential causal role for the high frequency hearing loss in tinnitus etiopathogenesis.

1. Introduction

Tinnitus is the perception of sound without a corresponding external source. Tinnitus can have many forms and various factors can contribute to its etiology. However, it is well established that hearing loss represents the most important risk factor for tinnitus [1]. The majority of tinnitus patients display increased hearing threshold in the pure-tone audiometry (PTA), particularly in the high frequency range [2–4]. Moreover the frequency spectrum of one individual's tinnitus corresponds to the frequency range of the hearing impairment [5, 6], thus underscoring the relevance of hearing loss as an etiologic factor for tinnitus. However, some tinnitus patients present without any detectable hearing loss in the frequency range of the conventional pure-tone audiometry (125 Hz–8 kHz) [7, 8]. It has been argued that a normal pure-tone audiogram (PTA) does not reliably preclude cochlear damage. Damage of hair cells coding for frequencies between the tested frequencies or above 8 kHz is not detected by the conventional audiometry. Accordingly, tinnitus patients with normal audiograms had more frequently cochlear dead regions [9] and outer hair cell damage and impaired hearing

thresholds in the extended high frequency region [10] as compared to control groups.

Furthermore, patients with tinnitus and normal audiograms demonstrated a significantly reduced amplitude of the wave I potential in the auditory brainstem response [7], suggesting damage of hair cells and/or auditory nerve fibers already at normal audiometric thresholds. Taken together these studies support the theory of a "hidden hearing loss" in tinnitus patients. However the question remains whether the high frequency audiometry should be recommended as a standard diagnostic procedure in the routine assessment of tinnitus patients [11]. One possible approach for answering this question is the investigation, how much additional clinical information is provided by the results of the HF-audiogram in tinnitus patients? For this purpose we investigated tinnitus patients with normal conventional PTA from the Tinnitus Research Initiative Database and contrasted the groups with normal and increased hearing thresholds in the HF-audiometry with respect to various clinical and demographic characteristics.

2. Material and Methods

Clinical, demographic, and audiometric data were obtained as part of the routine assessment at patient intake at the Interdisciplinary Tinnitus Center of the University of Regensburg, Germany, and collected in the Tinnitus Research Initiative Database [12]. Data were analysed from all patients presenting with chronic subjective tinnitus between 2007 and 2012, for which both conventional and HF PTA were available, who had normal hearing thresholds in the conventional PTA and who had given written informed consent for data recording and analyzing. The database studies are approved by the local institutional review board (ethical committee of the University of Regensburg).

The term "normal PTA" was defined as ≤15 dB HL over all frequencies from 125 Hz to 8 kHz [13]. The Tinnitus Sample Case History Questionnaire (TSCHQ) was used to gather clinical and demographical data of all patients [14]. Tinnitus severity was assessed by the German version of the Tinnitus Questionnaire (TQ) [15], the Tinnitus Handicap Inventory (THI) [16], and several numeric rating scales concerning tinnitus loudness/discomfort/annoyance/ignorability and unpleasantness. In addition, the Beck Depression Inventory (BDI) was used for quantification of depressive symptoms [17]. The audiological assessment included conventional PTA (125 Hz–8 kHz), HF-audiometry (at 10 kHz, 11.2 kHz, 12.5 kHz, 14 kHz, and 16 kHz), and matching of the tinnitus pitch. Audiometry and tinnitus matching were done with a Madsen Itera (GN Otometrics, Germany) audiometer with Sennheiser HDA-200 supra-aural headphones (Sennheiser electronic GmbH & Co. KG, Germany). The hearing threshold for all frequencies was determined by a standard Hughson-Westlake procedure (steps: 10 dB down, 5 dB up; 2 out of 3). The mean hearing level (dB HL) was calculated by averaging all thresholds for both ears measured in PTA from 125 Hz to 8 kHz. The same was done for the mean HF-hearing level (dB HL) for all frequencies from 10 kHz to 16 kHz. For tinnitus matching, the lower and upper bound frequency [Hz] of the tinnitus were assessed and the center frequency was determined as the geometric mean of both values.

Patients were divided into two groups: the first group included patients with normal thresholds in the HF-audiogram (≤15 dB HL over all frequencies) (HF-norm); the second group included patients with HF-hearing loss (HF-HL; hearing thresholds over 15 dB HL in at least one frequency). Those groups were compared with respect to gender, age, hearing threshold (range from 125 to 8 kHz), tinnitus severity (TQ, THI, and rating scales), depressive symptoms (BDI), tinnitus laterality, tinnitus duration, tinnitus pitch, presentation of selected somatic symptoms (headache, vertigo, temporomandibular disorder, neck pain, or other pain syndromes), and different triggers for tinnitus onset (loud blast of sound, whiplash, change in hearing, stress, and head trauma). Independent samples t-tests, chi-square tests, and Fisher exact tests were used for group comparisons. In addition, the relation between HF-audiogram asymmetry and tinnitus laterality was examined. For this purpose, the average of the HF-audiometry was calculated separately for the left and right ear. An asymmetry index was defined as the difference between the left and right ear with negative values indicating more pronounced hearing loss in the right ear and positive values indicating more pronounced hearing loss in the left ear. This asymmetry index was used as a dependent variable in an analysis of variance with laterality of tinnitus (measured in three categories: left ear, right ear, and bilateral/inside the head) as independent variable. Post hoc t-tests were controlled for multiple comparisons using a Bonferroni correction. All statistical tests were two-tailed. A value of $P < 0.05$ was used to determine statistical significance. Data in the text and tables are given as mean ± standard deviation.

3. Results

Data from 75 patients (61.5%; 43 men and 32 women; mean age 37.25 ± 10.25) with chronic tinnitus were analyzed. Thirteen of these patients (9 men and 4 women) had a normal HF-audiogram (see Table 1). The independent samples t-test comparing the HF-hearing level between both groups is highly significant, reconfirming the allocation of patients with normal versus pathological high frequency audiogram (see Table 1). The other group comparisons were significant for age, the tinnitus questionnaire, and tinnitus handicap inventory (see Table 1). Patients with pathological high frequency audiogram were significantly older and scored higher on the TQ and the THI in comparison to patients with normal high frequency audiogram. These significant results were confirmed, when the cutoff for a normal versus pathological high frequency audiogram was changed from 15 dB to 20 dB. If the cutoff was increased to 25 dB, the group difference in the TQ and THI did not reach significance level any more. The other results remained unchanged.

The ANOVA comparing the HF-audiogram asymmetry index for patients with left, right, and bilateral tinnitus was

Table 1: Demographic, audiologic, and clinical characteristics of patients with normal versus pathological HF-audiogram.

	N (HF-norm/HF-HL[1])	HF-norm	HF-HL	Group Comparison	
					P value
High frequency hearing level (dB HL)	75 (13/62)	2.69 ± 2.49	25.54 ± 12.25	$T(73) = -13.42$	>0.001*
Hearing level (dB HL)	75 (13/62)	3.27 ± 1.85	4.40 ± 2.23	$T(73) = -1.71$	0.092
Gender (m/f)	75 (13/62)	9/4	34/28	$\chi^2(1,75) = 0.910$	0.340
Age	75 (13/62)	24.63 ± 7.10	39.89 ± 8.74	$T(73) = -5.89$	>0.001*
BDI	70 (12/58)	7.85 ± 6.00	11.05 ± 9.89	$T(68) = -1.12$	0.267
Tinnitus severity					
TQ	75 (13/62)	23.85 ± 13.95	36.18 ± 17.18	$T(73) = -2.42$	0.018*
THI	74 (13/61)	33.69 ± 17.39	48.82 ± 23.61	$T(72) = -2.66$	0.014*
Strong/loud	73 (13/60)	4.85 ± 2.30	5.48 ± 2.31	$T(71) = -0.90$	0.370
Uncomfortable	73 (13/60)	6.00 ± 2.24	6.95 ± 2.52	$T(71) = -1.25$	0.214
Annoying	73 (13/60)	4.62 ± 2.40	5.97 ± 2.69	$T(71) = -1.67$	0.099
Unpleasant	73 (13/60)	4.85 ± 2.70	6.03 ± 2.74	$T(71) = -1.42$	0.160
Ignoring	73 (13/60)	5.08 ± 3.07	6.40 ± 2.90	$T(71) = -1.48$	0.144
Tinnitus characteristics					
Laterality (right/left/bilateral, in %)	74 (13/61)	38/31/31	28/31/41		0.691
Pitch	61 (9/52)	7334 ± 2378	7605 ± 4301	$T(59) = -0.18$	0.855
Duration (in months)	73 (13/60)	62.85 ± 95.76	67.68 ± 69.05	$T(71) = -0.21$	0.832
Onset of tinnitus related to no/yes in %					
Sound blast	65 (11/54)	82 /18	93/7		0.266
Whiplash	65 (11/54)	100/0	93/7		>0.999
Change in hearing	65 (11/54)	91/9	94/6		0.533
Stress	65 (11/54)	73/27	43/57		0.099
Head trauma	65 (11)	91/9	98/2		0.312
Others	65 (11)	27/73	48/52		0.320
Comorbidities of tinnitus (no/yes in %)					
Headache	71 (13)	77/23	52/48	$\chi^2(1,71) = 2.74$	0.098
Vertigo or dizziness	72 (13)	85/15	73/27		0.495
TMD	71 (13)	77/23	62/38		0.358
Neck pain	70 (13)	62/38	46/54	$\chi^2(1,70) = 1.07$	0.300
Other pain syndromes	71 (13)	92/8	69/31		0.162

Results from independent samples t-tests, chi-square tests and Fishers exact tests for group comparisons.
HF-norm: group with normal HF-audiogram; HF-HL: group with HF-hearing loss; m: male; f: female.
[1]Some information was not available for all patients.
*$\alpha < 0.05$.

Table 2: Asymmetry in high frequency audiogram for patients with left, right, and bilateral tinnitus.

Tinnitus laterality	N	Asymmetry index (left ear−right ear)
Left	23	5.04
Right	22	−0.95
Bilateral	29	−2.45

significant ($F(2, 71) = 4.76$; $P = 0.012$). Post hoc t-tests indicate a significant difference between patients with left and bilateral tinnitus ($P = 0.012$). Patients with left versus right ($P = 0.086$) and with right versus bilateral ($P > 0.99$) tinnitus did not differ significantly. As can be seen in Table 2, patients with left sided tinnitus show positive values in the asymmetry index indicating more high frequency hearing loss in the left ear. Patients with right sided and bilateral tinnitus show negative values, indicating more hearing loss in the right ear. More information about the composition of the asymmetry index can be found in Figure 1, where the average HF-hearing loss for patients with left, right, and bilateral tinnitus is depicted for both ears separately.

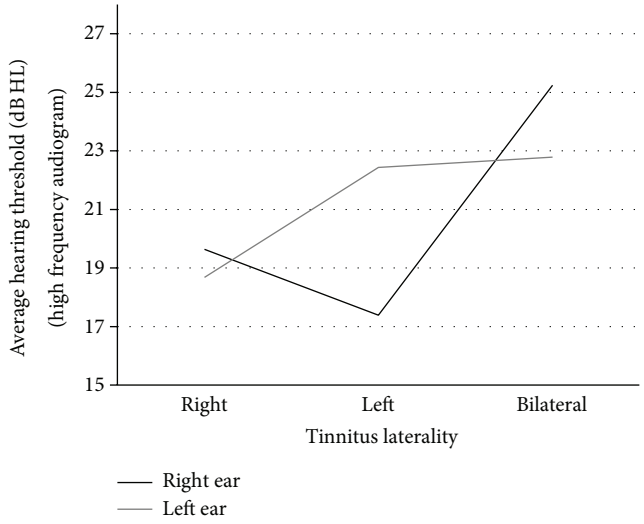


Figure 1: Tinnitus laterality and HF-hearing loss in the right and left ear.

4. Discussion

The association of chronic tinnitus and hearing loss is well established. Hearing loss is considered to be the most important risk factor for tinnitus [18] and a relationship between the laterality and pitch of tinnitus and the hearing loss could be demonstrated in several studies [3–5].

Since many patients report their tinnitus pitch in the high frequency range, it has been suggested that a comprehensive audiological assessment in tinnitus patients should include HF-audiometry [11]. The purpose of this study was to verify whether the results of the HF-audiometry would provide any additional clinically meaningful information in patients with normal conventional PTA.

First, we found that the majority of our tinnitus patients with normal audiogram had an abnormal HF-audiogram. This fits with earlier findings of increased abnormalities in the HF-audiogram [19] and in the HF otoacoustic emissions [20, 21] in tinnitus patients as compared to controls without tinnitus. Our findings also confirm the notion that the HF-audiometry is more sensitive for detecting hearing damage as compared to the standard audiometry [17, 22, 23]. This fits with our finding that in the HF-hearing loss group a tendency towards worse hearing thresholds in the standard PTA was observed. Given the sensitivity of HF PTA for detecting cochlear damage one may even consider extending the HF PTA to even higher frequencies.

Second, we found a relationship between tinnitus laterality and hearing asymmetry. Patients with left sided tinnitus had also more pronounced HF-hearing impairment on the left side, whereas patients with right sided and bilateral tinnitus had more pronounced HF-hearing impairment on the right side (Table 2). The correspondence between tinnitus laterality and hearing asymmetry for right and left sided tinnitus further confirms the assumption that hearing impairment is involved in tinnitus generation and supports the relevance of HF-audiometry in the diagnosis of tinnitus. The finding of right-accentuated HF-hearing loss in patients with bilateral tinnitus is unexpected and somewhat puzzling. If confirmed by future studies, it suggests that the pathophysiological mechanisms underlying bilateral tinnitus may be distinct from those of unilateral tinnitus. One might have had expected a higher tinnitus pitch in the group with HF-hearing loss. Indeed, in many patients with HF-hearing loss the tinnitus pitch was in the range of the hearing loss. Accordingly, the mean tinnitus pitch was higher in this group. However, due to the high variability of the tinnitus pitch in both groups, this difference did not reach significance level. The demonstration of impaired hearing threshold in the high frequency range in combination with the perception of a high-pitched tinnitus might reflect a very useful element in the counseling of tinnitus patients.

Third, we found that the mean age of the HF-norm group was lower than in the HF-HL group. This is not surprising, since a decline of hearing thresholds with increasing age is well known. The mean age of 24.6 years suggests that a normal HF-audiogram is almost exclusively found in relatively young tinnitus patients.

Fourth, we found higher scores in the TQ and THI questionnaires in the HF-HL group as compared to the HF-norm group. However, this finding should be interpreted with care since this difference did not reach significance any more when the cutoff for normal HF PTA was set at 25 dB HL. Earlier studies have reported higher tinnitus severity in tinnitus patients with more pronounced hearing impairment [24, 25]. In this context it is of interest that also hearing loss in the high frequency range, which should have no direct impact on verbal communication, may result in increased handicap.

One expectation was that other etiologic factors than hearing impairment would be more relevant in people with normal HF-audiometry. However, both groups did differ significantly neither in onset related events like whiplash or stress, nor in comorbidities like neck pain or temporomandibular problems. This may—similarly like the lack of a group difference in tinnitus pitch—be related to a lack of power in the relatively small sample. Moreover, it should be considered that a normal audiogram does not preclude cochlear impairment. Thus, in the group of tinnitus patients with normal standard and HF PTA, dead cochlear regions between the tested frequencies or damage to hair cells or neuronal fibers which are not threshold relevant cannot be excluded.

5. Conclusion

To summarize, the results of high frequency audiometry in tinnitus patients with normal conventional PTA are related to tinnitus laterality and tinnitus severity. These findings suggest that the HF-audiometry can be a useful complementary audiological test in a comprehensive diagnostic assessment of tinnitus patients. It should be recommended as a standard procedure in tinnitus patients of younger age including

children in the absence of clinical signs of hearing impairment. HF-audiometry might be of therapeutic value within the scope of counseling in explaining the etiopathogenesis of tinnitus to patients with normal conventional PTA but impaired high frequency hearing thresholds.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

This paper was presented at the 2013 AAO-HNSF Annual Meeting & OTO EXPO, September 29–October 2, 2013, Vancouver, BC, Canada.

References

[1] S. Ahlf, K. Tziridis, S. Korn, I. Strohmeyer, and H. Schulze, "Predisposition for and prevention of subjective tinnitus development," *PLoS ONE*, vol. 7, no. 10, Article ID e44519, 2012.

[2] D.-K. Kim, S.-N. Park, H. M. Kim et al., "Prevalence and significance of high-frequency hearing loss in subjectively normal-hearing patients with tinnitus," *Annals of Otology, Rhinology and Laryngology*, vol. 120, no. 8, pp. 523–528, 2011.

[3] O. König, R. Schaette, R. Kempter, and M. Gross, "Course of hearing loss and occurrence of tinnitus," *Hearing Research*, vol. 221, no. 1-2, pp. 59–64, 2006.

[4] F. Martines, D. Bentivegna, E. Martines, V. Sciacca, and G. Martinciglio, "Assessing audiological, pathophysiological and psychological variables in tinnitus patients with or without hearing loss," *European Archives of Oto-Rhino-Laryngology*, vol. 267, no. 11, pp. 1685–1693, 2010.

[5] A. Norena, C. Micheyl, S. Chéry-Croze, and L. Collet, "Psychoacoustic characterization of the tinnitus spectrum: implications for the underlying mechanisms of tinnitus," *Audiology and Neuro-Otology*, vol. 7, no. 6, pp. 358–369, 2002.

[6] M. Schecklmann, V. Vielsmeier, T. Steffens, M. Landgrebe, B. Langguth, and T. Kleinjung, "Relationship between audiometric slope and tinnitus pitch in tinnitus patients: insights into the mechanisms of tinnitus generation," *PLoS ONE*, vol. 7, no. 4, Article ID e34878, 2012.

[7] R. Schaette and D. McAlpine, "Tinnitus with a normal audiogram: physiological evidence for hidden hearing loss and computational model," *The Journal of Neuroscience*, vol. 31, no. 38, pp. 13452–13457, 2011.

[8] "Standard-Bezugspegel für die Kalibrierung audiometrischer Geräte," DIN EN ISO 389-1, 1998.

[9] N. Weisz, S. Müller, W. Schlee, K. Dohrmann, T. Hartmann, and T. Elbert, "The neural code of auditory phantom perception," *The Journal of Neuroscience*, vol. 27, no. 6, pp. 1479–1484, 2007.

[10] A. Fabijańska, J. Smurzyński, S. Hatzopoulos et al., "The relationship between distortion product otoacoustic emissions and extended high-frequency audiometry in tinnitus patients. Part 1: normally hearing patients with unilateral tinnitus," *Medical Science Monitor*, vol. 18, no. 12, pp. CR765–CR770, 2012.

[11] R. Goodey, "Tinnitus treatment: state of the art," *Progress in Brain Research*, vol. 166, pp. 237–246, 2007.

[12] M. Landgrebe, F. Zeman, M. Koller et al., "The Tinnitus Research Initiative (TRI) database: a new approach for delineation of tinnitus subtypes and generation of predictors for treatment outcome," *BMC Medical Informatics and Decision Making*, vol. 10, no. 1, article 42, 2010.

[13] International Organisation for Standardisation, "Akustik—Statistische Verteilung von Hörschwellen als eine Funktion des Alters," DIN EN ISO 7029, International Organisation for Standardisation, 1992.

[14] B. Langguth, R. Goodey, A. Azevedo et al., "Consensus for tinnitus patient assessment and treatment outcome measurement: tinnitus research initiative meeting, regensburg, July 2006," *Progress in Brain Research*, vol. 166, pp. 525–536, 2007.

[15] G. Goebel and W. Hiller, "The tinnitus questionnaire. A standard instrument for grading the degree of tinnitus. Results of a multicenter study with the tinnitus questionnaire," *HNO*, vol. 42, no. 3, pp. 166–172, 1994.

[16] C. W. Newman, S. A. Sandridge, and L. Bolek, "Development and psychometric adequacy of the screening version of the tinnitus handicap inventory," *Otology and Neurotology*, vol. 29, no. 3, pp. 276–281, 2008.

[17] R. R. Figueiredo, M. A. Rates, A. A. de Azevedo, P. M. de Oliveira, and P. B. A. de Navarro, "Correlation analysis of hearing thresholds, validated questionnaires and psychoacoustic measurements in tinnitus patients," *Brazilian Journal of Otorhinolaryngology*, vol. 76, no. 4, pp. 522–526, 2010.

[18] H. Hoffmann and G. Reed, "Epidemiology of tinnitus," in *Tinnitus: Theory and Management*, J. Snow, Ed., pp. 16–41, BC Decker, London, UK, 2004.

[19] H. J. Shim, S. K. Kim, C. H. Park et al., "Hearing abilities at ultra-high frequency in patients with tinnitus," *Clinical and Experimental Otorhinolaryngology*, vol. 2, no. 4, pp. 169–174, 2009.

[20] A. Fabijańska, J. Smurzyński, K. Kochanek, G. Bartnik, D. Raj-Koziak, and H. Skarzyński, "The influence of high frequency hearing loss on the distortion product otoacoustic emissions in tinnitus subjects with normal hearing threshold (0,25-8 kHz)," *Otolaryngologia Polska*, vol. 66, no. 5, pp. 318–321, 2012.

[21] A. Paglialonga, S. Fiocchi, L. del Bo, P. Ravazzani, and G. Tognola, "Quantitative analysis of cochlear active mechanisms in tinnitus subjects with normal hearing sensitivity: time-frequency analysis of transient evoked otoacoustic emissions and contralateral suppression," *Auris Nasus Larynx*, vol. 38, no. 1, pp. 33–40, 2011.

[22] N. Schmuziger, R. Probst, and J. Smurzynski, "Otoacoustic emissions and extended high-frequency hearing sensitivity in young adults," *International Journal of Audiology*, vol. 44, no. 1, pp. 24–30, 2005.

[23] N. Schmuziger, J. Patscheke, and R. Probst, "An assessment of threshold shifts in nonprofessional pop/rock musicians using conventional and extended high-frequency audiometry," *Ear and Hearing*, vol. 28, no. 5, pp. 643–648, 2007.

[24] B. Mazurek, H. Olze, H. Haupt, and A. J. Szczepek, "The more the worse: the grade of noise-induced hearing loss associates with the severity of tinnitus," *International Journal of Environmental Research and Public Health*, vol. 7, no. 8, pp. 3071–3079, 2010.

[25] R. Prestes and G. Daniela, "Impact of tinnitus on quality of life, loudness and pitch match, and high-frequency audiometry," *The International Tinnitus Journal*, vol. 15, no. 2, pp. 134–138, 2009.

Hindawi Publishing Corporation
BioMed Research International
Volume 2015, Article ID 975808, 7 pages
http://dx.doi.org/10.1155/2015/975808

Research Article

Efficacy and Safety of Repeated Courses of rTMS Treatment in Patients with Chronic Subjective Tinnitus

Astrid Lehner,[1,2] Martin Schecklmann,[1,2] Timm B. Poeppl,[1,2] Peter M. Kreuzer,[1,2] Juliette Peytard,[1,2] Elmar Frank,[1] and Berthold Langguth[1,2]

[1]*Department of Psychiatry and Psychotherapy, University of Regensburg, 93053 Regensburg, Germany*
[2]*Interdisciplinary Tinnitus Center, University of Regensburg, 93053 Regensburg, Germany*

Correspondence should be addressed to Astrid Lehner; astrid.lehner@medbo.de

Received 17 February 2015; Accepted 5 April 2015

Academic Editor: Aage R. Møller

Background. Repetitive transcranial magnetic stimulation (rTMS) has shown promising effects in the treatment of chronic subjective tinnitus. However, little is known about maintenance treatment in order to achieve long-lasting improvements. *Objective*. This study addresses the questions whether the repeated application of rTMS treatment can contribute to the maintenance or enhancement of treatment effects and if so in which cases repetitive treatment courses are beneficial. *Methods*. 55 patients with chronic tinnitus were treated with two rTMS treatment courses with ten treatment sessions each. The mean intertreatment interval was 20.65 ± 18.56 months. Tinnitus severity was assessed before and after each treatment course. *Results*. Both treatments were well tolerated and caused significant improvement of tinnitus severity. The main predictor for the outcome of the second treatment was the development of tinnitus distress in the phase between both treatment courses: the more patients worsened in this interval, the more they improved during the second treatment course. *Conclusion*. Repeated application of rTMS seems to be useful in tinnitus management and should preferentially be offered to patients who experience a worsening of their tinnitus during the intertreatment interval, irrespective of their response to the first treatment course.

1. Introduction

In the past decade, an increasing number of studies have examined the effectiveness of repetitive transcranial magnetic stimulation (rTMS) as a treatment option for chronic subjective tinnitus (for a review, see [1, 2]). Generally, the reduction of the tinnitus percept and distress after five to ten sessions of rTMS is reported to be mixed with respect to both duration and extent of improvement. While some studies indicate that the improvement vanishes after two weeks [3, 4], other studies observed rather long-lasting effects up to 4 years [5–7]. Likewise, while some patients report no or only little benefit, others improve a lot due to rTMS treatment. Besides this heterogeneous clinical improvement, the actual impact of rTMS treatment on the morphology of the brain seems to be of transient nature [8]. In any case, tinnitus is a chronic condition and the question arises what might be the next therapeutic step either if a patient still feels burdened by his tinnitus after a treatment attempt with rTMS or if the benefit of the treatment wanes over time. In these cases the repeated application of rTMS treatment might be useful. The idea to use repeated stimulation courses to maintain treatment effects is known from electroconvulsive therapy (ECT) of major depression, where immediate treatment effects are of temporary nature as well and where relapses of depressive symptoms are managed successfully by periodic repetition of ECT [9, 10]. Recently, it has even been debated whether rTMS could be used as maintenance method after an initial ECT therapy [11, 12]. Also, there already is some evidence for repeated rTMS treatments from studies examining the benefit of rTMS in patients with psychiatric or neurological disorders (for an overview, see [13]). In patients suffering from depression who had responded to an initial rTMS treatment, both the repetition of the whole treatment schedule after relapse of depressive symptoms [14, 15] and intensive monthly maintenance sessions to prevent the occurrence of

a relapse [16, 17] have been shown to be effective. Therefore, it is reasonable to assume that some kind of repeated rTMS treatment might also be useful in tinnitus management. Up to now there is little information on the effect of repeated rTMS therapies in tinnitus patients. Some case reports, small case series, and one study suggest that rTMS "booster" sessions might be effective as maintenance treatment for treatment responders and might even result in more pronounced tinnitus reduction than the initial treatment [13, 18–20]. Furthermore, maintenance treatment has been found to be well tolerated [13]. However, the sample sizes of those studies were small and only initial treatment responders were considered for repeated treatment. It remains unclear whether patients who had not responded to the initial treatment are "rTMS nonresponders" per se or whether they might benefit from rTMS treatment at some other point in time. As the effect of rTMS is known to be state-dependent [21], it is quite conceivable that a nonresponder might benefit from a second treatment course indeed. By presenting data of a large sample of patients who underwent two complete treatment courses of 10 days of rTMS, including both responders and nonresponders to the initial treatment, the current study tries to answer the questions whether (a) repeated courses of rTMS are safe, (b) whether they can contribute to the maintenance of treatment effects or may even enhance treatment response, and (c) in which cases a second treatment course might be beneficial.

2. Materials and Methods

Data from 55 patients (43 men, 12 women) with chronic subjective tinnitus were included in the analyses. Inclusion criteria were age over 18 years and chronic subjective tinnitus for at least 6 months. Exclusion criteria were treatable cause of tinnitus and all contraindications for rTMS treatment (pregnancy, epilepsy, cardiac pacemaker, head injury, and metal objects in or around the body which cannot be removed). Demographical data and clinical characteristics of the sample are given in Table 1. All patients underwent two complete treatment courses with each course consisting of ten sessions of rTMS on ten consecutive working days. Treatment was performed at the Tinnitus Center at the University of Regensburg, Germany. All patients provided written informed consent before both treatment courses. The first treatment course was done either in the context of a controlled clinical trial, open-label feasibility studies, or as compassionate use treatment. Part of the data of the first treatment course was therefore already published in the context of the respective study [22–28]. After the first treatment course, patients were informed about the option to repeat rTMS treatment but no appointments were made. This means that the patients decided for themselves if and when they wanted to repeat rTMS treatment. This could be after a worsening of symptoms, because patients hoped for an enhancement of their improvement or because former nonresponders wanted to retry rTMS treatment. The mean interval between both treatment courses was 20.65 ± 18.56 months.

Table 1: Demographical data and clinical characteristics of the sample.

Gender	43 males, 12 females
Age (years)	52.49 ± 11.42
Tinnitus duration (years)*	7.94 ± 7.15
Tinnitus laterality	5 right
	8 left
	12 both ears worse left
	8 both ears worse right
	19 both ears equally
	3 inside the head
Intertreatment interval (months)	20.65 ± 18.56
Identical treatment protocol for both treatment courses	30 yes, 25 no
TQ difference 1	−4.45 ± 10.13
TQ difference 2	−4.47 ± 8.23
TQ difference intertreatment interval	4.91 ± 14.42

Data are given as mean ± standard deviation.
*Before starting of first treatment course.

As data was collected over a long period of time (between 2003 and 2014), different treatment protocols were used (see Table 2). Each protocol contained low-frequency (1 Hz) rTMS of the left temporal or temporoparietal cortex with 2000 or 4000 stimuli per day. In the multisite protocols, additional high-frequency stimulation of the left dorsolateral prefrontal (20 Hz) or medial frontal cortex (10 Hz) or low-frequency stimulation of the right temporoparietal cortex (1 Hz) was involved. The high-frequency stimulation was always done first, followed by the low-frequency part. All treatment protocols were used in the context of clinical trials which had been approved by the local ethics committee. Localization of the stimulated areas was either done with a neuronavigational system or by using a standard procedure based on the 10–20 system [29–35]. Stimulation was applied with a Medtronic system with a classical figure-8-coil or, for the medial frontal stimulation, a double-cone-coil (Medtronic, Minneapolis, MN, USA). During treatment, the coil was held by a mechanical arm and the patients were seated comfortably in a reclining chair. Stimulation intensity was set at 110% of the individual resting motor threshold (RMT) for the figure-8-coil and 100% RMT for the double-cone-coil. RMT was defined as the minimal intensity at which motor evoked potentials were 50 μV in amplitude in the right abductor digiti minimi muscle for five out of ten stimulations [36]. Tinnitus distress was assessed before (baseline) and after (day 12) each treatment course using the German version of the tinnitus questionnaire (TQ, [37]).

IBM SPSS Statistics 22 (IBM Corporation, Armonk, NY) was used for data analyses. To test for changes in tinnitus severity due to rTMS treatment, paired t-tests were performed for the first and the second treatment course separately. For all further analyses, the difference of the TQ scores between baseline and day 12 was calculated with negative values indicating an improvement in tinnitus severity.

Table 2: Treatment protocols used in the first and second treatment courses.

	Number of patients treated	
	1st treatment	2nd treatment
Left temporal rTMS, 1 Hz, 2000 stimuli/day	19	10
Left temporal rTMS, 1 Hz, 4000 stimuli/day	4	—
Left temporal (1 Hz) plus left frontal (20 Hz) rTMS, 2000 stimuli/day	2	—
Left temporal (1 Hz) plus left frontal (20 Hz) rTMS, 4000 stimuli/day	22	31
Left and right temporoparietal (1 Hz) plus left frontal (20 Hz) rTMS, 4000 stimuli/day	5	13
Left temporoparietal (1 Hz) plus medial frontal (10 Hz), 4000 stimuli/day	3	1

Below, those difference scores are named "TQ difference 1" for the first treatment course and "TQ difference 2" for the second treatment course. Furthermore, the TQ difference of the intertreatment interval (ITI) was calculated to represent the development of tinnitus severity in the phase between both treatment courses ("TQ difference ITI"; baseline of the second treatment minus day 12 of the first treatment). To assess which patients benefit from a second treatment course, the following parameters were considered as possible predictors for TQ difference 2: TQ difference 1, the baseline score of the second treatment course, TQ difference ITI, the duration of the intertreatment interval (in months), and the change of treatment protocol from treatment one to treatment two (i.e., if the same protocol was used for both treatment courses, dummy coded). In a first step, all of those parameters were analysed with respect to their relation to TQ difference 2 using product-moment correlations for metric variables and a t-test for the discrete variable. All variables with significant influence on TQ difference 2 were entered as regressors into a multiple linear regression analysis (simultaneous model) where TQ difference 2 served as dependent variable. This was done in order to examine which regressors exert most influence if the other regressors are controlled for and to find out whether there are important interaction effects. Finally, in order to find out whether one of the different rTMS protocols was more effective than the others, analyses of variance (ANOVAs) were calculated. The TQ differences of the first or second treatment course were used as dependent variables and the rTMS protocols were used as independent variables (six protocols in the first treatment course, four protocols in the second treatment course; see Table 2). The level of significance was set at 0.05.

3. Results

All patients tolerated both treatment courses without any severe adverse effects. All treatments were completed as planned. Paired t-tests revealed that both the first and the second treatment course significantly reduced tinnitus severity as measured by the TQ (first treatment course $t(54) = 3.26$, $p = 0.002$; second treatment course $t(54) = 4.033$, $p < 0.001$). Please see Table 1 for mean and standard deviation of the TQ differences. Figure 1 shows the development of the TQ score over time. The t-test which was done to find out whether a change of treatment protocol from treatment one to treatment two had an influence on the outcome of the second treatment revealed no significant effect ($t(53) = -0.89$, $p = 0.376$). The product-moment correlations with TQ difference 2 were not significant for the duration of the intertreatment interval ($r = -0.167$, $p = 0.223$) and the baseline score of the second treatment course ($r = -0.128$, $p = 0.351$). In contrast, the correlations were significant for TQ difference 1 ($r = 0.282$, $p = 0.037$) and TQ difference ITI ($r = -0.475$, $p < 0.001$). Therefore, the latter two variables were entered as regressors in the linear regression analysis. Additionally, an interaction term between both variables was created by multiplying the centred variables. This term was also entered into the regression analysis. The TQ difference of the intertreatment interval significantly predicted the outcome of the second treatment course ($\beta = -0.452$, $t = -3.12$, and $p = 0.003$) while both TQ difference 1 ($\beta = 0.041$, $t = 0.28$, and $p = 0.780$) and the interaction term ($\beta = -0.013$, $t = -0.11$, and $p = 0.915$) were no significant predictors. Thus, TQ difference 1 loses its significant influence on TQ difference 2 if TQ difference ITI is controlled for. The overall model fit was $R^2 = 0.227$, $F(3, 51) = 5.00$, and $p = 0.004$. The scatter plot in Figure 2 shows the relation between TQ difference 2 and TQ difference ITI. The ANOVAs comparing the TQ differences obtained by the different treatment protocols turned out nonsignificant ($F(5, 49) = 0.37$; $p = 0.869$ for the first treatment course; $F(3, 51) = 1.48$, $p = 0.231$ for the second treatment course) indicating that none of the protocols was significantly superior (see Figure 3).

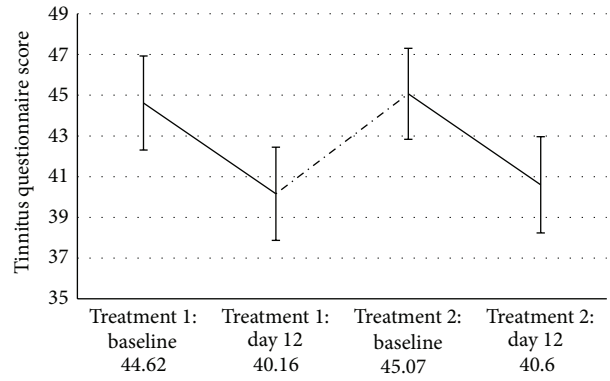


Figure 1: Change of the TQ score over time (mean ± standard error). The intertreatment interval is depicted as dashed line.

4. Discussion

This is the first study to examine repeated rTMS treatment courses in a rather large sample of tinnitus patients where responders as well as nonresponders of the initial treatment course were included. Both the first and the second treatment were well tolerated and led to a significant reduction of tinnitus severity. This finding confirms previous findings from smaller samples [13, 18, 19] and further supports the usefulness of repeated rTMS treatment for the management of chronic disorders like tinnitus. As can be seen in Figure 1, the average TQ scores decreased after the first treatment, increased in the intertreatment interval, and improved again during the second treatment course. These group data suggest that the beneficial effect of the first rTMS treatment vanishes over time during the intertreatment interval but can be renewed by repeated rTMS. The regression analysis provides additional insights. It reveals that TQ difference 2 is significantly related to both TQ difference 1 and TQ difference ITI. However, TQ difference 1 loses its significant influence if TQ difference ITI is controlled for. This means that the development of the TQ score during the intertreatment interval is a good predictor for the outcome of the second treatment course and that the outcome of the first treatment course provides hardly any additional predictive information. Consequently, a second treatment attempt might be most promising for patients who worsen between both treatment courses (see Figure 2), irrespective of the success of the first treatment. Interestingly enough, the baseline value of the second treatment is not significantly correlated with TQ difference 2. Thus, patients who worsen between both treatments do not have better outcomes to a second treatment course simply because they have higher baseline values. It was already observed previously that patients whose TQ score had increased in the period before initiation of rTMS benefited more than patients with prior improvement of tinnitus severity [27, 38]. One possible explanation for this effect is that the pretreatment changes in tinnitus severity might reflect a particular neurobiological condition of the brain which makes a response to rTMS more or less likely. As is known from former studies [21, 39, 40] the effect of rTMS depends on the state our brain is in when it is stimulated. Maybe, a worsening of tinnitus is accompanied by a neuronal activation pattern which makes the tinnitus brain more receptible to rTMS than a brain which is currently experiencing no change or improvement of tinnitus severity. This would also explain why the baseline score of the second treatment course, the duration of the intertreatment interval, and the change of the stimulation protocol did not correlate significantly with the outcome of the second treatment course—the baseline score alone tells us little about the process the brain is currently in—nor does the duration of the intertreatment interval. And a change of the stimulation protocol might only be promising if our brain is in a state susceptible to rTMS intervention and if the new protocol fits this state. This is only speculation, of course, and future controlled studies are needed to shed more light on the relation between the activational state of the tinnitus brain and its responsiveness to rTMS and to find out whether there are clinical markers (like the TQ difference of the intertreatment interval) which reflect such an advantageous state reliably.

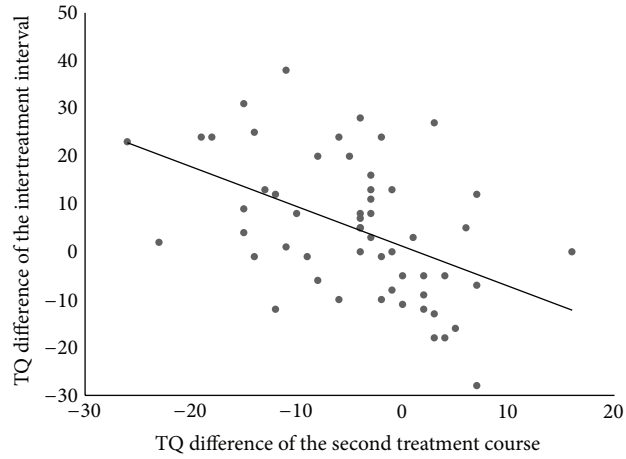
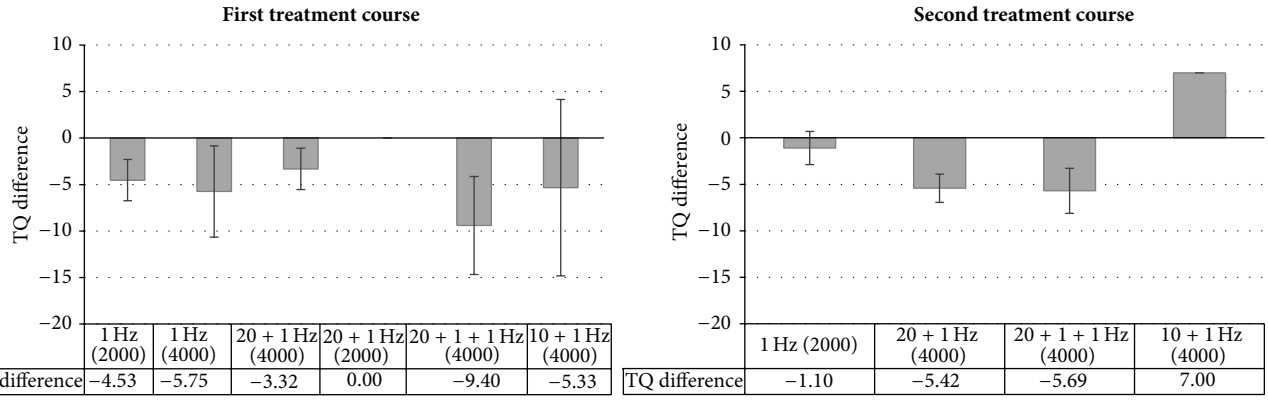


Figure 2: Point diagram showing the relation between the outcome of the second treatment course and the TQ difference of the intertreatment interval.

With respect to the repetition of rTMS treatment in general, the current study clearly shows that the second treatment course reduces tinnitus severity just as well as the first one. This is in line with former papers which also reported good response to maintenance treatment [13, 18, 19, 41]. As there are many possibilities as to when, how, and to whom repeated treatments can be offered, it is not surprising that past studies and case reports differ a lot regarding the strategy used for repeated rTMS treatments. In the current study, we decided to make as little specification of those variables as possible. This was done in order to be able to get an overall impression of repeated courses of rTMS for tinnitus patients and to find out which variables are of more or less importance for future studies. The only parameter that was determined in this study was the number of sessions: patients were treated with the full treatment course of ten sessions of rTMS. No fixed time schedule was used though but patients were retreated whenever they requested it. This design has the advantage that it reflects the typical clinical situation in which a patient presents for a repeated rTMS treatment. The correlation between the duration of the intertreatment interval and the outcome of the second treatment course was not significant, indicating that it might be not decisive for treatment response if repeated treatments are applied within few months after the first treatment attempt or after years.

Similar to the time schedule, the sample of patients for this study was also not determined beforehand. All previous studies only considered initial treatment responders for repeated rTMS courses, preventing the investigation of the question if the retreatment of a nonresponder is adequate. The present results show that also nonresponders might benefit from further rTMS treatment and that the response to the initial treatment is a good but not a sufficient predictor for the outcome of the second treatment course. Particularly if nonresponders experience a deterioration of their tinnitus, another treatment attempt might be reasonable.



	1 Hz (2000)	1 Hz (4000)	20 + 1 Hz (4000)	20 + 1 Hz (2000)	20 + 1 + 1 Hz (4000)	10 + 1 Hz (4000)
TQ difference	−4.53	−5.75	−3.32	0.00	−9.40	−5.33

	1 Hz (2000)	20 + 1 Hz (4000)	20 + 1 + 1 Hz (4000)	10 + 1 Hz (4000)
TQ difference	−1.10	−5.42	−5.69	7.00

Figure 3: Treatment outcomes (as measured by TQ differences) resulting from the different treatment protocols.

It turned out that the treatment protocols did not differ significantly with respect to treatment outcome neither in the first nor in the second treatment course. This is in line with past studies indicating that a superiority of combined protocols as compared with single-site protocols is not present immediately after rTMS treatment but only after a certain follow-up period (e.g., [22, 28]). As, in the current study, treatment outcome was only assessed directly after the last treatment session but not after a follow-up period, a difference between protocols was not to be expected.

The explorative character of our study entails limitations on the conclusions which can be drawn. Neither subjects nor experimenters were blinded regarding the second treatment course and the study lacks a wait list or placebo control group. Furthermore, there was a self-selection bias of patients who underwent the second rTMS treatment, and also the interval between the two treatment courses was not standardized. Therefore it cannot be exactly determined whether the observed effects are entirely rTMS specific and to which extent unspecific effects like a tendency to the mean may have contributed. Furthermore, the protocols used for rTMS treatment were not kept constant: six different protocols were used for the first treatment course and four different protocols for the second treatment course. Nevertheless, the results provide valuable information for future controlled trials which are clearly needed to investigate maintenance rTMS in more detail. In summary, this study demonstrated that (a) repeated courses of rTMS treatment cause a significant change of tinnitus severity and (b) the change of tinnitus severity during the intertreatment interval is a good predictor for treatment outcome of the second treatment course with patients whose tinnitus worsens during this interval benefitting most from the second treatment. It is particularly important to note that this is also true for initial nonresponders. If a further deterioration of their tinnitus happens, a repetition of rTMS treatment might definitely be reasonable in those patients.

5. Conclusions

Presenting a large sample of patients with chronic subjective tinnitus who were treated with two full courses of rTMS treatment, the current study shows that the repeated application of rTMS is well tolerated and represents a useful tool in tinnitus management. A second treatment attempt is especially promising for patients who had experienced a worsening of their tinnitus during the intertreatment interval. It is important to note that this relation is also true for patients who did not respond to the first treatment course: if those patients present with a deterioration of symptoms, they might benefit from a second treatment course indeed.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

The authors would like to thank Helene Niebling, Sandra Pfluegl, Ulrike Stadler, and Susanne Staudinger for their technical assistance in administering rTMS and collecting data.

References

[1] J. P. Lefaucheur, N. André-Obadia, A. Antal et al., "Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS)," *Clinical Neurophysiology*, vol. 125, no. 11, pp. 2150–2206, 2014.

[2] S. M. Theodoroff and R. L. Folmer, "Repetitive transcranial magnetic stimulation as a treatment for chronic tinnitus: a critical review," *Otology and Neurotology*, vol. 34, no. 2, pp. 199–208, 2013.

[3] C. Plewnia, M. Reimold, A. Najib, G. Reischl, S. K. Plontke, and C. Gerloff, "Moderate therapeutic efficacy of positron emission tomography-navigated repetitive transcranial magnetic stimulation for chronic tinnitus: a randomised, controlled pilot study," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 78, no. 2, pp. 152–156, 2007.

[4] S. Rossi, A. de Capua, M. Ulivelli et al., "Effects of repetitive transcranial magnetic stimulation on chronic tinnitus: a randomised, crossover, double blind, placebo controlled study," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 78, no. 8, pp. 857–863, 2007.

[5] J. Burger, E. Frank, P. Kreuzer et al., "Transcranial magnetic stimulation for the treatment of tinnitus: 4-year follow-up in treatment responders—a retrospective analysis," *Brain Stimulation*, vol. 4, no. 4, pp. 222–227, 2011.

[6] E. M. Khedr, J. C. Rothwell, and A. El-Atar, "One-year follow up of patients with chronic tinnitus treated with left temporoparietal rTMS," *European Journal of Neurology*, vol. 16, no. 3, pp. 404–408, 2009.

[7] T. Kleinjung, P. Eichhammer, B. Langguth et al., "Long-term effects of repetitive transcranial magnetic stimulation (rTMS) in patients with chronic tinnitus," *Otolaryngology—Head and Neck Surgery*, vol. 132, no. 4, pp. 566–569, 2005.

[8] A. Lehner, B. Langguth, T. B. Poeppl et al., "Structural brain changes following left temporal low-frequency rTMS in patients with subjective tinnitus," *Neural Plasticity*, vol. 2014, Article ID 132058, 10 pages, 2014.

[9] G. Petrides, K. G. Tobias, C. H. Kellner, and M. V. Rudorfer, "Continuation and maintenance electroconvulsive therapy for mood disorders: review of the literature," *Neuropsychobiology*, vol. 64, no. 3, pp. 129–140, 2011.

[10] K. Trevino, S. M. McClintock, and M. M. Husain, "A review of continuation electroconvulsive therapy: application, safety, and efficacy," *Journal of ECT*, vol. 26, no. 3, pp. 186–195, 2010.

[11] M. A. Cristancho, A. Helmer, R. Connolly, P. Cristancho, and J. P. O'Reardon, "Transcranial magnetic stimulation maintenance as a substitute for maintenance electroconvulsive therapy: a case series," *The Journal of ECT*, vol. 29, no. 2, pp. 106–108, 2013.

[12] Y. Noda, Z. J. Daskalakis, C. Ramos, and D. M. Blumberger, "Repetitive transcranial magnetic stimulation to maintain treatment response to electroconvulsive therapy in depression: a case series," *Frontiers in Psychiatry*, vol. 4, article 73, 2013.

[13] M. Mennemeier, T. Munn, M. Allensworth et al., "Laterality, frequency and replication of rTMS treatment for chronic tinnitus: pilot studies and a review of maintenance treatment," *Hearing Research*, vol. 295, pp. 30–37, 2013.

[14] P. B. Fitzgerald, J. Benitez, A. R. de Castella, T. L. Brown, Z. J. Daskalakis, and J. Kulkarni, "Naturalistic study of the use of transcranial magnetic stimulation in the treatment of depressive relapse," *Australian and New Zealand Journal of Psychiatry*, vol. 40, no. 9, pp. 764–768, 2006.

[15] A. Demirtas-Tatlidede, D. Mechanic-Hamilton, D. Z. Press et al., "An open-label, prospective study of repetitive transcranial magnetic stimulation (rTMS) in the long-term treatment of refractory depression: reproducibility and duration of the antidepressant effect in medication-free patients," *Journal of Clinical Psychiatry*, vol. 69, no. 6, pp. 930–934, 2008.

[16] P. B. Fitzgerald, N. Grace, K. E. Hoy, M. Bailey, and Z. J. Daskalakis, "An open label trial of clustered maintenance rTMS for patients with refractory depression," *Brain Stimulation*, vol. 6, no. 3, pp. 292–297, 2013.

[17] B. Langguth, M. Landgrebe, M. Zowe, M. Gerst, G. Hajak, and P. Eichhammer, "Repetitive transcranial magnetic stimulation for maintenance treatment of depression: a case report," *Journal of Clinical Psychiatry*, vol. 67, no. 5, pp. 835–836, 2006.

[18] M. Mennemeier, K. C. Chelette, J. Myhill et al., "Maintenance repetitive transcranial magnetic stimulation can inhibit the return of tinnitus," *Laryngoscope*, vol. 118, no. 7, pp. 1228–1232, 2008.

[19] B. Langguth, M. Landgrebe, G. Hajak, and T. Kleinjung, "In reference to maintenance repetitive transcranial magnetic stimulation can inhibit the return of tinnitus," *Laryngoscope*, vol. 118, no. 12, pp. 2264–2265, 2008.

[20] B. Langguth, P. Eichhammer, R. Wiegand et al., "Neuronavigated rTMS in a patient with chronic tinnitus. Effects of 4 weeks treatment," *NeuroReport*, vol. 14, no. 7, pp. 977–980, 2003.

[21] N. Weisz, L. Steidle, and I. Lorenz, "Formerly known as inhibitory: effects of 1-Hz rTMS on auditory cortex are state-dependent," *European Journal of Neuroscience*, vol. 36, no. 1, pp. 2077–2087, 2012.

[22] T. Kleinjung, P. Eichhammer, M. Landgrebe et al., "Combined temporal and prefrontal transcranial magnetic stimulation for tinnitus treatment: a pilot study," *Otolaryngology—Head and Neck Surgery*, vol. 138, no. 4, pp. 497–501, 2008.

[23] B. Langguth, M. Landgrebe, E. Frank et al., "Efficacy of different protocols of transcranial magnetic stimulation for the treatment of tinnitus: pooled analysis of two randomized controlled studies," *World Journal of Biological Psychiatry*, vol. 15, no. 4, pp. 276–285, 2014.

[24] T. Kleinjung, T. Steffens, M. Landgrebe et al., "Levodopa does not enhance the effect of low-frequency repetitive transcranial magnetic stimulation in tinnitus treatment," *Otolaryngology—Head and Neck Surgery*, vol. 140, no. 1, pp. 92–95, 2009.

[25] T. Kleinjung, T. Steffens, M. Landgrebe et al., "Repetitive transcranial magnetic stimulation for tinnitus treatment: no enhancement by the dopamine and noradrenaline reuptake inhibitor bupropion," *Brain Stimulation*, vol. 4, no. 2, pp. 65–70, 2011.

[26] B. Langguth, T. Kleinjung, E. Frank et al., "High-frequency priming stimulation does not enhance the effect of low-frequency rTMS in the treatment of tinnitus," *Experimental Brain Research*, vol. 184, no. 4, pp. 587–591, 2008.

[27] A. Lehner, M. Schecklmann, M. Landgrebe et al., "Predictors for rTMS response in chronic tinnitus," *Frontiers in Systems Neuroscience*, vol. 6, article 11, 2012.

[28] A. Lehner, M. Schecklmann, T. B. Poeppl et al., "Multisite rTMS for the treatment of chronic tinnitus: stimulation of the cortical tinnitus network—a pilot study," *Brain Topography*, vol. 26, no. 3, pp. 501–510, 2013.

[29] R. E. Hoffman, N. N. Boutros, S. Hu, R. M. Berman, J. H. Krystal, and D. S. Charney, "Transcranial magnetic stimulation and auditory hallucinations in schizophrenia," *The Lancet*, vol. 355, no. 9209, pp. 1073–1075, 2000.

[30] H. H. Jasper, "The ten-twenty electrode system of the International Federation," *Electroencephalography and Clinical Neurophysiology*, vol. 10, no. 2, pp. 371–375, 1958.

[31] B. Langguth, M. Zowe, M. Landgrebe et al., "Transcranial magnetic stimulation for the treatment of tinnitus: a new coil positioning method and first results," *Brain Topography*, vol. 18, no. 4, pp. 241–247, 2006.

[32] U. Herwig, P. Satrapi, and C. Schönfeldt-Lecuona, "Using the international 10–20 EEG system for positioning of transcranial magnetic stimulation," *Brain Topography*, vol. 16, no. 2, pp. 95–99, 2003.

[33] R. E. Hoffman, K. A. Hawkins, R. Gueorguieva et al., "Transcranial magnetic stimulation of left temporoparietal cortex and medication-resistant auditory hallucinations," *Archives of General Psychiatry*, vol. 60, no. 1, pp. 49–56, 2003.

[34] U. Herwig, F. Padberg, J. Unger, M. Spitzer, and C. Schönfeldt-Lecuona, "Transcranial magnetic stimulation in therapy studies: examination of the reliability of 'standard' coil positioning by neuronavigation," *Biological Psychiatry*, vol. 50, no. 1, pp. 58–61, 2001.

[35] E. Frank, P. Eichhammer, J. Burger et al., "Transcranial magnetic stimulation for the treatment of depression: feasibility and

results under naturalistic conditions: a retrospective analysis," *European Archives of Psychiatry and Clinical Neuroscience*, vol. 261, no. 4, pp. 261–266, 2011.

[36] P. M. Rossini, A. T. Barker, A. Berardelli et al., "Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee," *Electroencephalography and Clinical Neurophysiology*, vol. 91, no. 2, pp. 79–92, 1994.

[37] G. Goebel and W. Hiller, "The tinnitus questionnaire. A standard instrument for grading the degree of tinnitus. Results of a multicenter study with the tinnitus questionnaire," *HNO*, vol. 42, no. 3, pp. 166–172, 1994.

[38] P. M. Kreuzer, M. Landgrebe, M. Schecklmann et al., "Can temporal repetitive transcranial magnetic stimulation be enhanced by targeting affective components of tinnitus with frontal rTMS? A randomized controlled pilot trial," *Frontiers in Systems Neuroscience*, vol. 5, article 88, 2011.

[39] H. R. Siebner, N. Lang, V. Rizzo et al., "Preconditioning of low-frequency repetitive transcranial magnetic stimulation with transcranial direct current stimulation: evidence for homeostatic plasticity in the human motor cortex," *Journal of Neuroscience*, vol. 24, no. 13, pp. 3379–3385, 2004.

[40] N. Lang, H. R. Siebner, D. Ernst et al., "Preconditioning with transcranial direct current stimulation sensitizes the motor cortex to rapid-rate transcranial magnetic stimulation and controls the direction of after-effects," *Biological Psychiatry*, vol. 56, no. 9, pp. 634–639, 2004.

[41] J. L. Dornhoffer and M. Mennemeier, "Using repetitive transcranial magnetic stimulation for the treatment of tinnitus," *Hearing Journal*, vol. 63, no. 11, pp. 16–20, 2010.

Hindawi Publishing Corporation
BioMed Research International
Volume 2015, Article ID 797416, 7 pages
http://dx.doi.org/10.1155/2015/797416

Research Article

Tinnitus and Headache

Berthold Langguth,[1] Verena Hund,[1] Volker Busch,[1] Tim P. Jürgens,[2] Jose-Miguel Lainez,[3] Michael Landgrebe,[1,4] and Martin Schecklmann[1]

[1]*Department of Psychiatry and Psychotherapy, University of Regensburg, 93049 Regensburg, Germany*
[2]*Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, 20246 Hamburg, Germany*
[3]*Department of Neurology, Catholic University of Valencia, 46010 Valencia, Spain*
[4]*Department of Psychiatry, Psychosomatics and Psychotherapy, Kbo-Lech-Mangfall-Klinik Agatharied, 83734 Hausham, Germany*

Correspondence should be addressed to Berthold Langguth; berthold.langguth@medbo.de

Received 6 May 2015; Accepted 21 July 2015

Academic Editor: Martin Kompis

Background. Tinnitus and headache are frequent disorders. Here, we aimed to investigate whether the occurrence of headache among tinnitus patients is purely coincidental or whether tinnitus and headache are pathophysiologically linked. We investigated a large sample of patients with tinnitus and headache to estimate prevalence rates of different headache forms, to determine the relationship between tinnitus laterality and headache laterality, and to explore the relationship between tinnitus and headache over time. *Method*. Patients who presented at a tertiary referral center because of tinnitus and reported comorbid headache were asked to complete validated questionnaires to determine the prevalence of migraine and tension-type headache and to assess tinnitus severity. In addition, several questions about the relationship between headache and tinnitus were asked. *Results*. Datasets of 193 patients with tinnitus and headache were analysed. 44.6% suffered from migraine, 13% from tension-type headache, and 5.7% from both. Headache laterality was significantly related to tinnitus laterality and in the majority of patients fluctuations in symptom severity of tinnitus and headache were interrelated. *Conclusion*. These findings suggest a significant relationship between tinnitus and headache laterality and symptom interaction over time and argue against a purely coincidental cooccurrence of tinnitus and headache. Both disorders may be linked by common pathophysiological mechanisms.

1. Introduction

Tinnitus is defined as the perception of sounds in the absence of a corresponding acoustic signal. It is a frequent disorder, which is reported by about 10% of the population [1]. While some patients can habituate or learn to ignore the phantom sound, others are severely impaired by their tinnitus. Previous research has shown that comorbidities such as hyperacusis [2], hearing loss [3], insomnia [4], depression [5, 6], pain syndromes [7], and headache [8, 9] play a major role in tinnitus-related impairment in quality of life [10]. Tinnitus-related impairment in quality of life can be measured by specific validated tinnitus questionnaires such as the "Tinnitus Questionnaire" [11] or the "Tinnitus Handicap Inventory" [12], but also by numeric rating scales [13, 14].

Like in headaches, idiopathic and secondary forms of tinnitus can be distinguished [15]. Several pathologies can cause both symptomatic headache and tinnitus, such as carotid artery dissections [16, 17], arteriovenous malformations, traumatic brain injury, space occupying intracranial lesions, and intracranial hypo- or hypertension [18]. Interestingly, many patients with idiopathic tinnitus report headache syndromes as well [18, 19]. Since both idiopathic headaches and idiopathic tinnitus are frequent disorders [20, 21], this could be purely coincidental. However, a large population-based epidemiological study in elderly people identified a history of migraine as clinical risk factor for the development of tinnitus and suggested an interrelation between tinnitus and headache syndromes [22].

Moreover, there is increasing evidence that some forms of idiopathic headaches and tinnitus share similar pathophysiological mechanisms. Both animal studies and human imaging studies found that tinnitus is related to abnormal activity in the central auditory pathways as a consequence

of auditory deafferentation [23–25]. In addition to activity changes in central auditory pathways, alterations in a complex network of attention-, emotion-, and memory-related brain areas have been demonstrated [15, 26] resembling changes in a similar network of cortical areas in chronic pain [23–25, 27]. Moreover, it has been proposed that pain, headache, and tinnitus overlap in their pathophysiological mechanism by sharing specific alterations in thalamocortical activity [28–32]. These neurophysiological alterations which can be detected as specific changes of oscillatory activity by magneto- or electroencephalography have been described with the term thalamocortical dysrhythmia [29].

More recently, animal studies have demonstrated that trigeminal input interacts at the dorsal cochlear nucleus with the activity of central auditory pathways [33] and tinnitus perception, as assessed by behavioural tests [34]. Further support for an involvement of the trigeminal system in tinnitus pathophysiology derives from the clinical observation that many patients can modulate tinnitus activity by face and jaw movements [35, 36]. Moreover, an association between temporomandibular joint disorders and tinnitus [37, 38] is well established and successful treatment of temporomandibular joint disorders was shown to improve tinnitus [39]. Naturally, an abnormal function of the peripheral and central parts of the trigeminal system is a prerequisite for the formation of primary and secondary headaches, as has been shown in migraine [40] and trigeminal autonomic headaches [41]. Finally, recent studies identified shared pivotal clinical symptoms in Meniere's disease and vestibular migraine such as episodic hearing impairment, tinnitus, and vertigo [42, 43]. Thus, both the central pain processing network (also referred to as the "pain matrix") and the trigeminal system represent a common link in the pathophysiology of idiopathic headache syndromes and tinnitus.

To further investigate a potential relationship between idiopathic headache and tinnitus, we asked patients who presented at the multidisciplinary Tinnitus Center at the University of Regensburg and who reported the existence of headaches in the Tinnitus Case History Questionnaire [44] to complete a headache questionnaire [45, 46] and to answer additional questions about the relationship between tinnitus and headache.

In detail, we aimed (1) to estimate prevalence rates of different headache forms among tinnitus patients, (2) to investigate whether there is a relationship between tinnitus laterality and headache laterality in patients with unilateral tinnitus and unilateral headache, and (3) to explore the relationship between tinnitus and headache over time.

2. Methods and Materials

2.1. Sample. The cross-sectional observational study was based on datasets of all patients aged between 18 and 90, who presented to the multidisciplinary Tinnitus Center of the University of Regensburg between 2003 and 2011 and whose data were included in the Tinnitus Research Initiative database [47]. All patients who reported the existence of headaches in the Tinnitus Case History Questionnaire (answer "yes" to the question, "Do you suffer from headaches?") [44] were contacted by mail and asked to complete additional questionnaires. Informed consent was obtained before inclusion into the study. The study was approved by the ethics committee of the University of Regensburg (11-101-0286). All data were pseudonymised before further analysis.

2.2. Assessment of Headaches and Tinnitus Severity. In addition to the information available from the Tinnitus Research database [47], the actual tinnitus severity was quantified by the Tinnitus Questionnaire (TQ; Goebel 1994). According to the TQ score tinnitus severity can be classified as mild (0–30), moderate (31–46), severe (47–59), and extreme (60–84).

For classification of headaches, the diagnostic headache questionnaire of Fritsche et al. [45] was used, which was developed and validated to meet the diagnostic criteria for migraine and tension-type headache, 2nd version of the classification criteria of the International Headache Society (ICHD-2). The questionnaire enables differentiating migraine, tension-type headache, cluster headache, combination of migraine and tension-type headache, combination of tension-type and cluster headache, and nonclassifiable headache with very good test-retest reliability (0.95). Validation of the questionnaire in a tertiary headache clinic [48] and in a population-based sample [46] revealed that sensitivity and specificity of the questionnaire are sufficient to diagnose migraine and tension-type headache, but not trigeminal autonomic cephalgias.

Additional questions regarding headache frequency, headache medication, and the temporal relationship between tinnitus and headache were asked (Table 1; questions are provided in Supplementary Material available online at http://dx.doi.org/10.1155/2015/797416). Questions 29 and 30 of the Supplementary Material asked whether the onset of tinnitus influenced headache and vice versa. We combined these two questions into one variable whether beginning of the second symptom influenced the first symptom.

2.3. Statistical Analysis. The frequencies of the different headache forms and of the mutual interaction between tinnitus and headache in the sample were analysed descriptively. The relationship between tinnitus laterality and headache laterality was analysed by a Chi-square test of independence. The influence of a mutual interaction between tinnitus and headache on tinnitus severity was analysed by a one-factorial ANOVA. In case of significant results Fisher's least significant difference (LSD) *post hoc* tests were performed. A p value of < 0.05 was regarded as statistically significant.

3. Results

489 out of 1817 patients reported headaches in the Tinnitus Case History Questionnaire. All these 489 patients were contacted. 225 (46%) answered and 193 datasets were analyzed (for more information, see Figure 1).

The 193 participating patients (117 (60.6%) female, 52 ± 12 years) suffered for 97.3 ± 110.1 months from their tinnitus; their TQ score was 45.5 ± 18.3. 79 patients suffered from unilateral or predominantly unilateral tinnitus (51 left-sided,

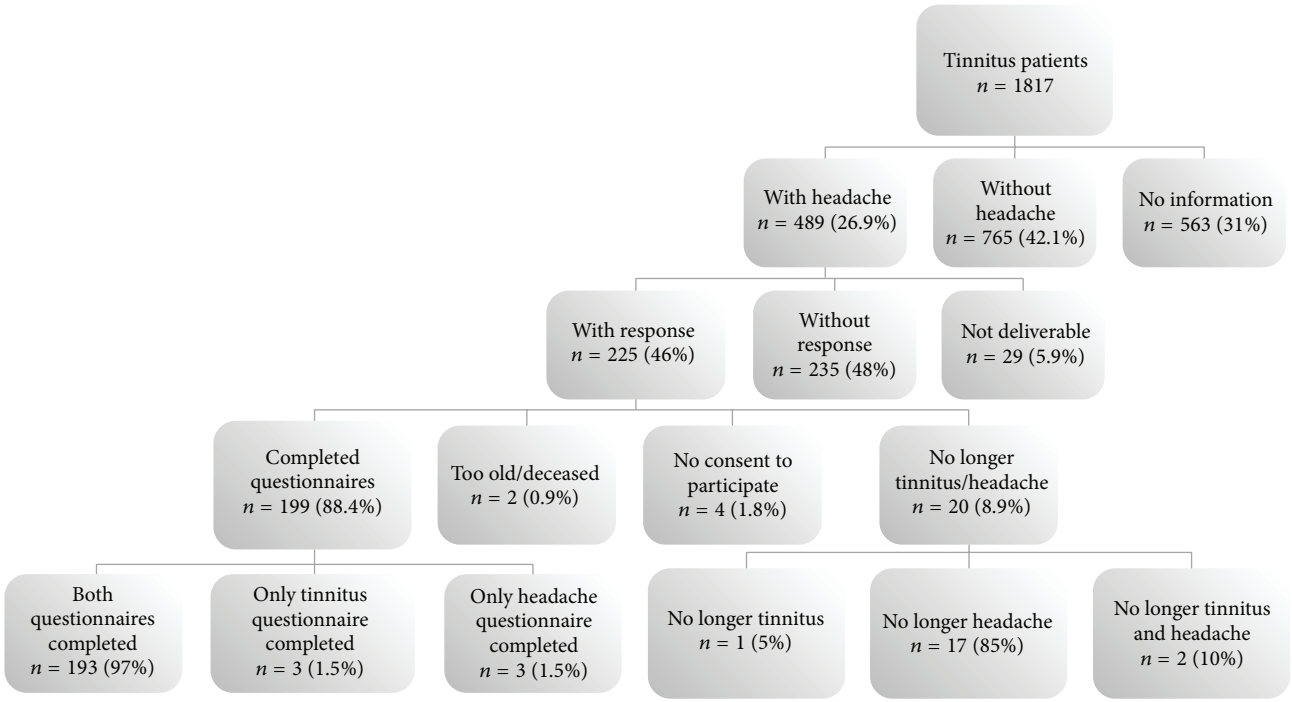


Figure 1: Data flow diagram of the questionnaire survey.

Table 1: Prevalence and clinical characteristics of the different headache types (according to the questionnaire classification of Fritsche et al. (2007) [45]).

Headache type	*N* (% of whole sample)	Chronic (% of all patients with this headache form)	Episodic (% of all patients with this headache form)	Days with headache/month	Patients with medication intake (% of all patients with this headache form)	Days with medication intake/month
Migraine	86 (45%)	14 (16.3%)	72 (83.7%)	9.9 ± 9.3	66 (77%)	8.6 ± 11.9
Tension-type headache	25 (13%)	7 (28%)	18 (72%)	12.8 ± 8.7	16 (64%)	5.1 ± 3.5
Trigeminal autonomic headache	8 (4%)	1 (12.5%)	7 (87.5%)	8.5 ± 5.8	7 (87.5%)	13.7 ± 27.2
Migraine and tension-type headache	11 (6%)	Migraine: 2 (18.2%) Tension-type headache: 3 (27.3%)	Migraine: 9 (81.8%) Tension-type headache: 8 (72.7%)	13.1 ± 10.0	8 (73%)	7.6 ± 7.0
Nonclassifiable headache	63 (33%)	n.a.	n.a.	7.8 ± 6.9	43 (68.2%)	8.4 ± 8.6

28 right-sided); in 111 patients, the tinnitus was either on both sides or in the head (nonunilateral); three patients provided no information concerning tinnitus laterality.

According to the headache questionnaire, 86 (45%) patients suffered from migraine, 25 (13%) from tension-type headache, 8 (4%) from trigeminal autonomic headache, 11 (6%) from migraine and tension-type headache, and 63 (33%) from nonclassifiable headache (for more details about clinical headache characteristics, see Table 1).

There was a significant relationship between headache and tinnitus laterality ($\chi^2 = 15.490$; df = 4; $p = 0.004$), even if among the headache types only the trigeminal autonomic headache is strictly side-locked. In all nonunilateral, left-sided, and right-sided tinnitus, the corresponding headache types were more frequently encountered (see Figure 2).

When asked about onset of tinnitus and headache, 67 (34.7%) patients reported tinnitus onset before headache onset, 106 (54.9%) patients reported headache onset before tinnitus onset, and 20 (10.4%) patients reported simultaneous onset. 101 (57.4%) patients reported that the onset of the second symptom did not influence the first; 60 (34.1%) patients reported worsening of the first symptom and in 15

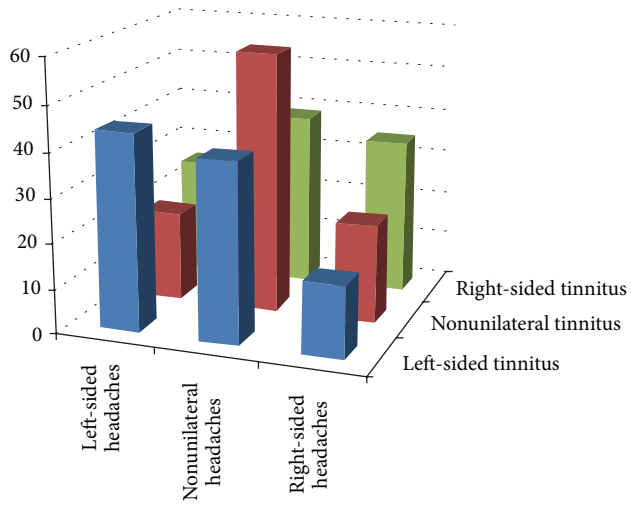


Figure 2: Prevalence rates of patients with headache laterality depending on tinnitus laterality (displayed as percent of all patients with a given tinnitus laterality). In all nonunilateral, left-sided, and right-sided tinnitus, the corresponding headache types were more frequently encountered.

(8.5%) the second symptom attenuated the first symptom. These three groups differed significantly in their TQ scores ($F = 9.077$; df = 2,162; $p < 0.001$) with the highest TQ scores in those patients in which the second symptom either increased (TQ: 50.93 ± 18.96; $p < 0.001$) or attenuated (TQ: 55.43 ± 13.12; $p = 0.003$) the first symptom, as compared to those without any change (TQ: 40.13 ± 17.65).

Asked about an ongoing relationship between tinnitus and headache, 82 (43.4%) reported that worsening of tinnitus was related to worsening of headaches and vice versa, and 9 (4.8%) patients reported an inverse relation (worsening of tinnitus related to improvement in headaches and vice versa). 79 (41.8%) reported no and 19 (10.1%) another relationship between tinnitus and headaches. Patients with an ongoing relationship between tinnitus and headache had higher TQ scores (positive relationship: 49.48 ± 16.76; inverse relationship: 45.44 ± 13.99; another relationship: 46.59 ± 19.04) than those without such a relationship (39.47 ± 19.06). ANOVA showed a significant main effect ($F = 4.002$; df = 3,173; $p = 0.009$) with a significant difference between the group with positive association and the group with no association ($p = 0.001$).

4. Discussion

In order to explore a potential relationship between tinnitus and headache we systematically investigated the occurrence of different headache types in a large sample of tinnitus patients. For this purpose, we used a self-report questionnaire, which has previously been used as a screening instrument in an epidemiological study in Germany [20] and in a study that analysed the relationship between headache and low-back pain [49]. In our sample of tinnitus patients, the proportion of tension-type headaches (19% of all headache patients) was clearly lower than the proportion of tension-type headache in the general population (44% of all headache patients [20]). The proportion of migraine patients in our sample was similar to that in the general population (50% of all headache patients in our sample as compared to 52% of all headache patients in the general population [20]) whereas unclassifiable headaches were slightly more frequent than in the general population (33% in our sample as compared to 26% in the general population [20]).

Our results demonstrate the feasibility to assess headache subtypes among tinnitus patients by using self-report questionnaires. However, we are also well aware about the shortcomings of the chosen approach. First, in the comparison of prevalence rates between our sample and the population-based survey, it has to be considered that the prevalence of the different headache forms depends strongly on age and gender, but the age and gender distribution of the tinnitus sample is not representative of the population. Second, we cannot exclude a selection bias and a reporting bias, since we only contacted tinnitus patients, who had presented at a tertiary tinnitus clinic and who had reported the existence of headaches, when they presented at the tinnitus clinic. Third, the retrospective design and the symptom assessment by questionnaires may be confounded by a recall bias. Fourth we received completed questionnaires only from about half of the patients, who had presented with tinnitus and headache in our clinic. The main reason for this relatively low response rate may have been that the interval between presentation in the clinic and contacting the patients was up to eight years.

Because of these limitations in a next step our findings should be complemented by case-control or population-based studies with prospective design and additional clinical examination to confirm prevalence rates of different headache forms among tinnitus patients. Also patient samples presenting in headache clinics should be investigated for the presence of tinnitus to obtain complementary information from patients in whom headache is the primary symptom. Face-to-face interviews will enable a higher diagnostic accuracy especially in patients with trigeminal autonomic cephalgias, in whom the validated questionnaire has only limited specificity [46, 48].

To our knowledge, our study is the first that studied the local and temporal relationship between headache and tinnitus in detail. Here we found a highly significant association between tinnitus laterality and headache laterality. An even higher correlation might be obtained by asking explicitly for side changes of headaches and tinnitus, which we did not do in this study. It may also be warranted to specifically screen for vestibular migraine, which may mimic Meniere's disease [42] and which can cause both tinnitus and headache.

With respect to symptom onset, more patients reported that headache onset preceded tinnitus rather than the opposite and only a small proportion reported that both symptoms started simultaneously. These findings were expected as headache typically starts at earlier age than tinnitus.

Thus, we observed a highly significant association between tinnitus and headache localisation and various possible temporal associations of the onset of the two symptoms. These data fit with the assumption that headache and tinnitus

are linked via common pathophysiological mechanisms. As headache precedes tinnitus in the majority of cases one could assume that headache can trigger tinnitus. But tinnitus can also trigger headache or a third factor may predispose to local susceptibility (e.g., left, right, or nonunilateral). Thus, one could imagine that a unilateral headache syndrome results in sensitization of the trigeminal system, which then facilitates the development of tinnitus. Also the opposite direction (unilateral tinnitus sensitizing the trigeminal system and resulting in headache on the same side) is possible. Finally the susceptibility to both symptoms may be caused by a third factor, for example, a unilateral trigeminal pathology, a globally increased sensitivity for nonunilateral headache and tinnitus in the context of a somatization disorder, or an increased genetic susceptibility for developing thalamocortical dysrhythmia [29]. Further electrophysiological and neuroimaging studies will be needed to identify the neuronal link between both disorders.

About half of the asked patients reported that fluctuations in the symptoms are related to each other. In the vast majority of these cases worsening of one symptom went along with worsening of the other symptom, but there were also cases with a reciprocal interaction or a more complex relationship. Such a relationship of symptom severity over time is a further indicator for a pathophysiological link between tinnitus and headache. Patients reporting such a relationship had a significantly higher tinnitus severity as compared to patients where fluctuations of tinnitus and headache were not related. Since a relationship of the two symptoms over time can only be detected, if symptoms are fluctuating, the result is confounded by the existence of symptom fluctuations. Further studies are needed to distinguish whether fluctuations *per se* are related with higher symptom severity or whether it is the interrelation between headache and tinnitus that is responsible for higher tinnitus severity. It might be of particular interest to investigate those patients who reported a reciprocal interaction between tinnitus and headache, since the mechanisms of this interaction may provide hints for potential therapeutic interventions. While an increase of tinnitus during migraine attacks has been reported earlier [50, 51], a reciprocal interaction has not yet been described before.

In summary our findings of a significant relationship between tinnitus and headache laterality and a temporal interaction of both disorders in the majority of cases suggest that the cooccurrence of tinnitus and headache is not purely coincidental but that both disorders may be linked by shared pathophysiological mechanisms.

Conflict of Interests

The authors have no conflict of interests, financial or otherwise, related directly or indirectly to the submitted work.

Acknowledgments

The authors thank Susanne Staudinger and Sandra Pfluegl for their assistance with data management.

References

[1] H. J. Hoffman and G. W. Reed, "Epidemiology of tinnitus," in *Tinnitus: Theory and Management*, J. B. Snow, Ed., pp. 16–41, BC Decker, London, UK, 2004.

[2] M. Schecklmann, M. Landgrebe, B. Langguth et al., "Phenotypic characteristics of hyperacusis in tinnitus," *PLoS ONE*, vol. 9, no. 1, Article ID e86944, 2014.

[3] B. Mazurek, H. Olze, H. Haupt, and A. J. Szczepek, "The more the worse: the grade of noise-induced hearing loss associates with the severity of tinnitus," *International Journal of Environmental Research and Public Health*, vol. 7, no. 8, pp. 3071–3079, 2010.

[4] T. Crönlein, B. Langguth, P. Geisler, and G. Hajak, "Tinnitus and insomnia," *Progress in Brain Research*, vol. 166, pp. 227–233, 2007.

[5] B. Langguth, T. Kleinjung, B. Fischer, G. Hajak, P. Eichhammer, and P. G. Sand, "Tinnitus severity, depression, and the big five personality traits," *Progress in Brain Research*, vol. 166, pp. 221–225, 2007.

[6] B. Langguth, M. Landgrebe, T. Kleinjung, G. P. Sand, and G. Hajak, "Tinnitus and depression," *World Journal of Biological Psychiatry*, vol. 12, no. 7, pp. 489–500, 2011.

[7] P. M. Kreuzer, M. Landgrebe, M. Schecklmann et al., "Trauma-associated tinnitus: audiological, demographic and clinical characteristics," *PLoS ONE*, vol. 7, no. 9, Article ID e45599, 2012.

[8] P. Lindberg, L. Lyttkens, L. Melin, and B. Scott, "Tinnitus—incidence and handicap," *Scandinavian Audiology*, vol. 13, no. 4, pp. 287–291, 1984.

[9] S. I. Erlandsson, L. R. M. Hallberg, and A. Axelsson, "Psychological and audiological correlates of perceived tinnitus severity," *International Journal of Audiology*, vol. 31, no. 3, pp. 168–179, 1992.

[10] B. Langguth, "A review of tinnitus symptoms beyond 'ringing in the ears': a call to action," *Current Medical Research and Opinion*, vol. 27, no. 8, pp. 1635–1643, 2011.

[11] R. S. Hallam, S. C. Jakes, and R. Hinchcliffe, "Cognitive variables in tinnitus annoyance," *British Journal of Clinical Psychology*, vol. 27, no. 3, pp. 213–222, 1988.

[12] C. W. Newman, G. P. Jacobson, and J. B. Spitzer, "Development of the tinnitus handicap inventory," *Archives of Otolaryngology—Head and Neck Surgery*, vol. 122, no. 2, pp. 143–148, 1996.

[13] F. Zeman, M. Koller, B. Langguth et al., "Which tinnitus-related aspects are relevant for quality of life and depression: results from a large international multicentre sample," *Health and Quality of Life Outcomes*, vol. 12, article 7, 2014.

[14] I. Adamchic, B. Langguth, C. Hauptmann, and P. A. Tass, "Psychometric evaluation of visual analog scale for the assessment of chronic tinnitus," *The American Journal of Audiology*, vol. 21, no. 2, pp. 215–225, 2012.

[15] B. Langguth, P. M. Kreuzer, T. Kleinjung, and D. De Ridder, "Tinnitus: causes and clinical management," *The Lancet Neurology*, vol. 12, no. 9, pp. 920–930, 2013.

[16] V. Biousse, J. D'Anglejan-Chatillon, H. Massiou, and M.-G. Bousser, "Head pain in non-traumatic carotid artery dissection: a series of 65 patients," *Cephalalgia*, vol. 14, no. 1, pp. 33–36, 1994.

[17] B. Langguth and T. Kleinjung, "Tinnitus," *MMW Fortschritte der Medizin*, vol. 153, no. 48, p. 40, 2011.

[18] A. M. J. P. Lainez and A. Ponz, "Tinnitus with headaches," in *Textbook of Tinnitus*, A. L. B. Moller, D. De Riddeer, and T. Kleinjung, Eds., pp. 487–490, Springer, New York, NY, USA, 2011.

[19] B. Rubinstein, A. Axelsson, and G. E. Carlsson, "Prevalence of signs and symptoms of craniomandibular disorders in tinnitus patients," *Journal of Craniomandibular Disorders*, vol. 4, no. 3, pp. 186–192, 1990.

[20] M.-S. Yoon, Z. Katsarava, M. Obermann et al., "Prevalence of primary headaches in Germany: results of the German Headache Consortium Study," *Journal of Headache and Pain*, vol. 13, no. 3, pp. 215–223, 2012.

[21] J. Shargorodsky, G. C. Curhan, and W. R. Farwell, "Prevalence and characteristics of tinnitus among US adults," *The American Journal of Medicine*, vol. 123, no. 8, pp. 711–718, 2010.

[22] D. Sindhusake, M. Golding, P. Newall, G. Rubin, K. Jakobsen, and P. Mitchell, "Risk factors for tinnitus in a population of older adults: the blue mountains hearing study," *Ear and Hearing*, vol. 24, no. 6, pp. 501–507, 2003.

[23] J. J. Eggermont and L. E. Roberts, "The neuroscience of tinnitus," *Trends in Neurosciences*, vol. 27, no. 11, pp. 676–682, 2004.

[24] D. De Ridder, A. B. Elgoyhen, R. Romo, and B. Langguth, "Phantom percepts: tinnitus and pain as persisting aversive memory networks," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 108, no. 20, pp. 8075–8080, 2011.

[25] D. De Ridder, S. Vanneste, N. Weisz et al., "An integrative model of auditory phantom perception: tinnitus as a unified percept of interacting separable subnetworks," *Neuroscience and Biobehavioral Reviews*, vol. 44, pp. 16–32, 2014.

[26] C. P. Lanting, E. De Kleine, and P. Van Dijk, "Neural activity underlying tinnitus generation: results from PET and fMRI," *Hearing Research*, vol. 255, no. 1-2, pp. 1–13, 2009.

[27] A. May, "New insights into headache: an update on functional and structural imaging findings," *Nature Reviews Neurology*, vol. 5, no. 4, pp. 199–209, 2009.

[28] M. Moazami-Goudarzi, L. Michels, N. Weisz, and D. Jeanmonod, "Temporo-insular enhancement of EEG low and high frequencies in patients with chronic tinnitus. QEEG study of chronic tinnitus patients," *BMC Neuroscience*, vol. 11, article 40, 2010.

[29] R. R. Llinás, U. Ribary, D. Jeanmonod, E. Kronberg, and P. P. Mitra, "Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 96, no. 26, pp. 15222–15227, 1999.

[30] M. de Tommaso, A. Ambrosini, F. Brighina et al., "Altered processing of sensory stimuli in patients with migraine," *Nature Reviews Neurology*, vol. 10, no. 3, pp. 144–155, 2014.

[31] D. De Ridder, S. Vanneste, B. Langguth, and R. Llinas, "Thalamocortical dysrhythmia: a theoretical update in tinnitus," *Frontiers in Neurology*, vol. 6, article 124, 2015.

[32] S. Schmidt, J. R. Naranjo, C. Brenneisen et al., "Pain ratings, psychological functioning and quantitative EEG in a controlled study of chronic back pain patients," *PLoS ONE*, vol. 7, no. 3, Article ID e31138, 2012.

[33] S. Shore, J. Zhou, and S. Koehler, "Neural mechanisms underlying somatic tinnitus," *Progress in Brain Research*, vol. 166, pp. 107–123, 2007.

[34] S. D. Koehler and S. E. Shore, "Stimulus timing-dependent plasticity in dorsal cochlear nucleus is altered in tinnitus," *Journal of Neuroscience*, vol. 33, no. 50, pp. 19647–19656, 2013.

[35] R. A. Levine, "Somatic (craniocervical) tinnitus and the dorsal cochlear nucleus hypothesis," *The American Journal of Otolaryngology—Head and Neck Medicine and Surgery*, vol. 20, no. 6, pp. 351–362, 1999.

[36] T. G. Sanchez, G. C. Yupanque Guerra, M. C. Lorenzi, A. L. Brandão, and R. F. Bento, "The influence of voluntary muscle contractions upon the onset and modulation of tinnitus," *Audiology and Neuro-Otology*, vol. 7, no. 6, pp. 370–375, 2002.

[37] V. Vielsmeier, T. Kleinjung, J. Strutz, R. Bürgers, P. M. Kreuzer, and B. Langguth, "Tinnitus with temporomandibular joint disorders: a specific entity of tinnitus patients?" *Otolaryngology—Head and Neck Surgery*, vol. 145, no. 5, pp. 748–752, 2011.

[38] V. Vielsmeier, J. Strutz, T. Kleinjung et al., "Temporomandibular joint disorder complaints in Tinnitus: further hints for a putative Tinnitus subtype," *PLoS ONE*, vol. 7, no. 6, Article ID e38887, 2012.

[39] R. Buergers, T. Kleinjung, M. Behr, and V. Vielsmeier, "Is there a link between tinnitus and temporomandibular disorders?" *Journal of Prosthetic Dentistry*, vol. 111, no. 3, pp. 222–227, 2014.

[40] S. Akerman and M. Romero-Reyes, "Insights into the pharmacological targeting of the trigeminocervical complex in the context of treatments of migraine," *Expert Review of Neurotherapeutics*, vol. 13, no. 9, pp. 1041–1059, 2013.

[41] A. May, "Diagnosis and clinical features of trigeminoautonomic headaches," *Headache*, vol. 53, no. 9, pp. 1470–1478, 2013.

[42] B. A. Neff, J. P. Staab, S. D. Eggers et al., "Auditory and vestibular symptoms and chronic subjective dizziness in patients with Ménière's disease, vestibular migraine, and Ménière's disease with concomitant vestibular migraine," *Otology and Neurotology*, vol. 33, no. 7, pp. 1235–1244, 2012.

[43] J. A. Lopez-Escamez, J. Dlugaiczyk, J. Jacobs et al., "Accompanying symptoms overlap during attacks in Menière's disease and vestibular migraine," *Frontiers in Neurology*, vol. 5, article 265, 2014.

[44] B. Langguth, R. Goodey, A. Azevedo et al., "Consensus for tinnitus patient assessment and treatment outcome measurement: Tinnitus Research Initiative meeting, Regensburg, July 2006," *Progress in Brain Research*, vol. 166, pp. 525–536, 2007.

[45] G. Fritsche, M. Hueppe, M. Kukava et al., "Validation of a German language questionnaire for screening for migraine, tension-type headache, and trigeminal autonomic cephalgias," *Headache*, vol. 47, no. 4, pp. 546–551, 2007.

[46] M.-S. Yoon, M. Obermann, G. Fritsche et al., "Population-based validation of a German-language self-administered headache questionnaire," *Cephalalgia*, vol. 28, no. 6, pp. 605–608, 2008.

[47] M. Landgrebe, F. Zeman, M. Koller et al., "The Tinnitus Research Initiative (TRI) database: a new approach for delineation of tinnitus subtypes and generation of predictors for treatment outcome," *BMC Medical Informatics and Decision Making*, vol. 10, no. 1, article 42, 2010.

[48] J. Chatkin, L. Fritscher, C. de Abreu et al., "Exhaled carbon monoxide as a marker for evaluating smoking abstinence in a Brazilian population sample," *Primary Care Respiratory Journal*, vol. 16, no. 1, pp. 36–40, 2007.

[49] M.-S. Yoon, A. Manack, S. Schramm et al., "Chronic migraine and chronic tension-type headache are associated with concomitant low back pain: results of the German Headache Consortium study," *Pain*, vol. 154, no. 3, pp. 484–492, 2013.

[50] R. W. Evans and G. Ishiyama, "Migraine with transient unilateral hearing loss and tinnitus," *Headache*, vol. 49, no. 5, pp. 756–758, 2009.

[51] M. Volcy, F. D. Sheftell, S. J. Tepper, A. M. Rapoport, and M. E. Bigal, "Tinnitus in migraine: an allodynic symptom secondary to abnormal cortical functioning?" *Headache*, vol. 45, no. 8, pp. 1083–1087, 2005.

Hindawi Publishing Corporation
BioMed Research International
Volume 2015, Article ID 569052, 8 pages
http://dx.doi.org/10.1155/2015/569052

Clinical Study

Acoustic Coordinated Reset Neuromodulation in a Real Life Patient Population with Chronic Tonal Tinnitus

Christian Hauptmann,[1] Armin Ströbel,[2] Mark Williams,[3] Nitesh Patel,[3] Hannes Wurzer,[4] Tatjana von Stackelberg,[5] Uwe Brinkmann,[6] Berthold Langguth,[7] and Peter A. Tass[1,8,9]

[1]*Institute of Neuroscience and Medicine-Neuromodulation (INM-7), Jülich Research Center, 52425 Jülich, Germany*
[2]*CERES GmbH Evaluation & Research, 79539 Lörrach, Germany*
[3]*The Tinnitus Clinic Inc., London W1G 6AX, UK*
[4]*Tinnitus Zentrum Promenadeplatz, 80333 München, Germany*
[5]*Ear, Nose and Throat (ENT) Center, 40667 Meerbusch, Germany*
[6]*Ear, Nose and Throat (ENT) Clinic Hamm-Ahlen-Oelde, 59302 Oelde, Germany*
[7]*Department of Psychiatry and Psychotherapy, University of Regensburg, 93053 Regensburg, Germany*
[8]*Department of Neurosurgery, Stanford University, Stanford, CA 94305, USA*
[9]*Department of Neuromodulation, University of Cologne, 50923 Cologne, Germany*

Correspondence should be addressed to Christian Hauptmann; c.hauptmann@fz-juelich.de

Received 3 November 2014; Accepted 11 January 2015

Academic Editor: Aage R. Møller

Purpose. Primary tinnitus has a severe negative influence on the quality of life of a significant portion of the general population. Acoustic coordinated reset neuromodulation is designed to induce a long-lasting reduction of tinnitus symptoms. To test acoustic coordinated reset neuromodulation as a treatment for chronic, tonal tinnitus under real life conditions, an outpatient study "RESET Real Life" was commissioned by ANM GmbH. Herein we present the results of this study. *Methods*. In a prospective, open-label, nonrandomized, noncontrolled multicenter clinical study with 200 chronic tinnitus patients, tinnitus questionnaire TBF-12 and Global Clinical Improvement-Impression Scale (CGI-I7) are used to study the safety and efficacy of acoustic coordinated reset neuromodulation. 189 patients completed the last 12-month visit, 11 patients dropped out (8 because of nontreatment related reasons; 2 because tinnitus did not change; and 1 because tinnitus got louder). *Results*. Acoustic coordinated reset neuromodulation caused a statistically and clinically significant decrease in TBF-12 scores as well as in CGI-I7 after 12 months of therapy under real life conditions. There were no persistent adverse events reported that were related to the therapy. *Conclusion*. The field study "RESET Real Life" provides evidence for safety and efficacy of acoustic coordinated reset neuromodulation in a prospective, open-label, real life setting.

1. Introduction

The perception of sound in the absence of a corresponding sound source is the definition of primary tinnitus, which, in its chronic form, affects 10–15% of the general population in industrialized countries [1]. About 2% are severely impaired in their quality of life because of chronic tinnitus and rely on professional help [2, 3].

A growing body of evidence suggests that altered spectral power of neural signals, that is altered statistical distribution of power over frequency, as measured by EEG/MEG, is the neuronal fingerprint of primary tinnitus [4–10] and that the perception of tinnitus requires the involvement of a larger network of brain areas [11–14]. There are now several reports of oscillatory brain activity changes, recorded via EEG, in tinnitus patients that reveal a decrease in alpha wave power (10–14 Hz) within the primary auditory cortices [4, 9] and an increase in slow wave delta activity (1.5–4 Hz) [4, 9, 15] when compared to controls. Slow wave oscillations have been attributed to hyperpolarization of thalamic nuclei as

a result of auditory deafferentation, which may enhance thalamocortical oscillations thus inducing pathological neural synchrony that has been proposed as the progenitor of tinnitus perception [16].

Various approaches have been investigated for the treatment of primary tinnitus [17] such as cognitive behavioral therapy [18], hearing aids [19], sound maskers [20], tinnitus retraining therapy [21], medication [22–24], hyperbaric oxygen therapy [25], acupuncture [26], and neuromodulation [27]. However, meta-analytic evidence has only been found for a beneficial effect from cognitive behavioral therapy on quality of life of tinnitus patients but not on tinnitus loudness [18].

Acoustic CR neuromodulation is a noninvasive acoustic stimulation therapy for primary tonal tinnitus, which was developed computationally [28–30]. The therapy is designed to counteract pathological neural synchrony by sustainably reducing the strength of synaptic connectivity between neurons within an affected cell population [8, 14]. In order to target the synchronized focus in the tonotopically organized auditory cortex, four acoustic tones are delivered with different frequencies centered around the characteristic frequency of the patient's tinnitus percept [8]. This approach aims to reduce pathologically enhanced neural synchrony within the primary auditory cortices which, in turn, results in a net decrease in effective connectivity across the global brain network involved in tinnitus perception [9, 14] along with a decrease of tinnitus-related abnormal cross-frequency coupling [31]. The tonotopically targeted stimulation tones are presented to the patient via a handheld tone generator (T30 CR neurostimulator), which utilizes earphones that are adapted from receiver-in-the-ear-canal (RIC) hearing aids. These RIC adapted earphones ensure that the patient's external auditory meatus is not occluded by the headphone receiver and enables a high degree of acoustic environmental transparency during stimulation tone presentation.

First evidence for acoustic CR neuromodulation as being an effective therapy for primary tonal tinnitus was provided by a randomized proof of concept trial: a statistically and clinically significant improvement in tinnitus questionnaire (TQ) and visual analogue scale (VAS) for loudness/annoyance scores was obtained [8, 32, 33]. Furthermore, the analysis of EEG recordings demonstrated a change in pathologically altered EEG power (i.e., α, γ, and δ band) towards normalization [8, 9].

To consolidate the results from the RESET proof of concept study in a larger patient population and in a real life outpatient setting, a second study, named RESET Real Life (RRL, ClinicalTrials.gov: NCT01435317) was conducted. The goal of the interventional multicenter RRL study was to collect data for the confirmation of efficacy and safety of twelve months of acoustic CR neuromodulation as a treatment of chronic tinnitus using the CE marked therapy system T30 CR. Tinnitus burden was assessed with the TBF-12 [34]; tinnitus loudness and annoyance were measured with numeric rating scales (NRS, ranging from 0 to 100) and clinical global improvement with the CGI-I7. In total, 200 patients were included in this prospective, open-label, nonrandomized, noncontrolled multicenter study at 23 study sites. Herein, we present the final data after 12 months of therapy.

2. Materials

200 patients were enrolled in this multicenter clinical study on Acoustic CR neuromodulation between November 2011 and May 2012 in 23 study centers run by ENT specialists located in Germany. Inclusion criteria were symptomatic primary tonal chronic tinnitus (≥3 months), <60 dB hearing loss for all tested frequencies (125 Hz–8 kHz), and men and women ≥ 18 years old. Patients were not included in the study if they were found to be suffering from serious neurologic, psychiatric, or otological disease, objective tinnitus (e.g., tinnitus caused by muscle movements, vascular noise, and other somatosounds), Meniere's disease, and tinnitus triggered by craniomandibular disorders.

Regular visits took place 0.5, 1, 2, 3, 6, 9, and 12 months after treatment start. The mean age of the patients was 50.6 years at study start, and 76.3% of the patients were male (Table 1). 62.1% of patients had undergone two or more tinnitus treatments prior to acoustic CR neuromodulation without significant relief. Among them 18.7% of patients had undergone more than 5 previous tinnitus treatments. Only 15.2% of patients were treated with Acoustic CR neurostimulation as a first line therapy. Most of the patients (68.2%) suffered from bilateral tinnitus (see Table 1).

Subjects were asked what they believe was responsible for inducing their tinnitus. We are aware about the limited reliability of subjective causal attributions to tinnitus onset. Nevertheless, the answer to this question provides some orientation about individual etiologic factors [35, 36]. 19 (9.5%) patients responded that it is noise trauma, 22 (10.9%) hearing problems, 95 (47.3%) stress, and 65 (32.8%) other reasons (multiple responses were allowed). The tinnitus severity (based on the initial TBF-12 measurement) was *slight (no handicap)* for 31.8% (TBF-12 0–8 pts), *mild* for 34.4% (TBF-12 9–12 pts), *moderate* for 24.1% (TBF-12 13–17 pts), and *severe* for 9.7% of the patients (TBF-12 18–24 pts). Tinnitus duration was less than six month for 2.0%, between six months and four years for 32.0%, between four years and ten years for 29.4%, and more than ten years for 36.6% of the patients. 43.1%/11.3% showed no hearing impairment (averaged/maximal hearing impairment ≤20 dBHL), 52.8%/19.5% a mild hearing impairment (averaged/maximal hearing impairment between 20 dBHL and 40 dBHL), 4.1%/42.0% a moderate hearing impairment (averaged/maximal hearing impairment between 40 dBHL and 60 dBHL), and 0.0%/27.2% a severe hearing impairment (averaged/maximal hearing impairment >60 dBHL).

The treatment with acoustic CR neuromodulation required regular visits to ENT clinics. At the first visit, a thorough pitch matching process was carried out to determine the tinnitus frequency. Based on the evaluated tinnitus frequency f_T, four stimulation tones were defined, two below and two above the individual tinnitus frequency (frequency range: $[0.76 f_T : 1.4 f_T]$). The amplitudes of the stimulation tones were adjusted in order to ensure that

Table 1: Demographic data of study population.

Gender	
male	151 (76.3%)
female	47 (23.7%)
Age	
mean (std.)	50.6 yrs (10.4)
Perception of tinnitus	
unilateral	63 (31.8%)
bilateral	135 (68.2%)
Pretreatment	
none	30 (15.2%)
one	45 (22.7%)
≥two	123 (62.1%)
Cause of tinnitus	
noise trauma	19 (9.5%)
hearing problems	22 (10.9%)
stress	95 (47.3%)
Tinnitus severity	
slight (no handicap)	62 (31.8%)
mild	67 (34.4%)
moderate	47 (24.1%)
severe	19 (9.7%)
Tinnitus duration	
<6 months	4 (2.0%)
6 months to 4 years	63 (32.0%)
4 years to 10 years	58 (29.4%)
>10 years	72 (36.6%)
Hearing impairment 250 Hz–8.000 Hz (averaged/maximal)	
≤20 dBHL	84 (43.1%)/22 (11.3%)
20 dBHL–40 dBHL	103 (52.8%)/38 (19.5%)
40 dBHL–60 dBHL	8 (4.1%)/82 (42.0%)
>60 dBHL	0 (0.0%)/53 (27.2%)

The information concerning the cause of tinnitus is based on a self-assessment of the patient and the tinnitus severity is based on the TBF-12 scores (missing values are not taken into account, the total number of subjects varies between variables, and percentages are calculated without taking missing values into account). Hearing impairment is listed with two values: the averaged hearing impairment (in dBHL as measured by pure tone audiometry as described in DIN EN ISO 8253-1 within the range from 250 Hz to 8.000 Hz), for example, averaged over all frequencies of the audiogram, and the maximal hearing impairment, for example, the maximal impairment observed at one frequency.

all tones were comfortably audible, at the same subjective loudness level, and slightly above the patient's hearing threshold.

With this information (frequency and amplitude of stimulation tones), the handheld T30 CR device was programmed with a randomized tone sequence which consisted of the repetitive application of the four stimulation tones with a repetition rate of 1.5 Hz. Short pauses within the stimulation signal (CycOn = 3, CycOff = 2) are utilized in order to enhance the process of unlearning pathological tinnitus activity [37]. The stimulation pattern containing the four stimulation frequencies is designed to induce a phase reset of abnormal delta oscillations at different locations within the tonotopically organized auditory cortex (see Figure 1).

The therapy was applied using the T30 CR neurostimulator, which consists of a programmable, battery-powered device combined with a customized, open fit earphone that utilizes a receiver-in-the-ear-canal (RIC) technology. The prescribing clinician uses propriety software to program the T30 CR neurostimulator. The patients were asked to use their T30 CR neurostimulator device every day for 4–6 hours, applying the therapy signals either continuously or splitting up the stimulation time into sessions not shorter than one hour. Visits to the ENT clinic took place at the beginning of the therapy and then 0.5, 1, 2, 3, 6, 9, and 12 months after beginning of the therapy. At each visit to the ENT clinic, the tinnitus tone was measured by a thorough pitch matching process and the device was reprogrammed when the tinnitus tone was found to have changed.

The primary outcome measure of the study is the analysis of changes in tinnitus severity, measured by the German version of tinnitus handicap inventory (TBF-12, *Tinnitus-Beeinträchtigungs-Fragebogen*) or improvement of the Clinical Global Impression-Improvement Scale (CGI-I7). Improvement was defined as a statistically significant ($P < 0.05$) reduction of scores comparing baseline values to end of treatment (visit after 12 months). All scores were obtained in the off-stimulation situation.

The TBF-12 tinnitus handicap inventory consists of 12 questions leading to a total score of 24 points (worst result). Scores were categorized depending on the score recorded: *slight (no handicap)* (0–8 pts), *mild handicap* (9–12 pts), *moderate handicap* (13–17 pts), and *severe handicap* (18–24 pts) [38]. CGI-I7 consists of the seven categories: *very much improved*, *much improved*, *slightly improved*, *no change*, *slightly worse*, *much worse*, and *very much worse,* expressed by the numbers 1 to 7 (1 equals the *very much improvement category*).

For the final analysis, outcome measurements for the full 12 months of therapy were analyzed. For the statistical analyses the *t*-test was utilized to evaluate the TBF-12 and the sign test to evaluate the CGI-I7. This final analysis reports the results of the primary (TBF-12, CGI-17) and secondary endpoints (numeric rating scale (NRS) for tinnitus loudness and annoyance). Additionally, the patients were asked to report their device usage pattern to allow for the assessment of compliance.

The *t*-tests were applied as paired, one sided, equal variances, equal sample size tests to TBF-12 (total score), NRS loudness, and NRS annoyance. Scores before and after treatment were compared. Null hypothesis was the acquisition of equal mean scores before and after treatment. Alternative hypothesis was the acquisition of smaller means after treatment. The sign test was applied to CGI. CGI was grouped in 2 categories "improvement" and "equal/worse." Null hypothesis was the acquisition of same number of patients in "improvement" and "equal/worse" category. Alternative hypothesis was more patients in the "improvement" category. Significance

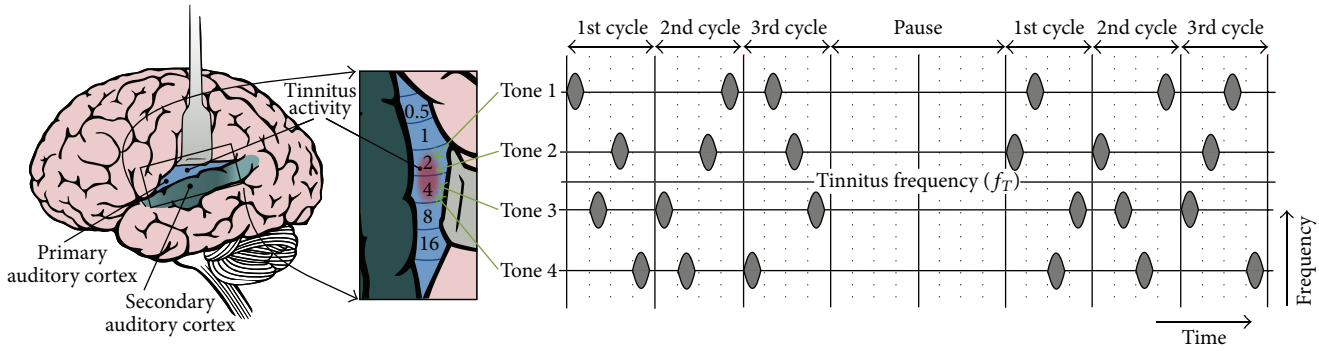


Figure 1: Stimulation signal of acoustic CR neuromodulation.

level was set to 0.05. No multiple testing corrections were applied. Missing values in the data were treated as missing for the analysis. Data from drop-out patients was treated by LOCF (last observation carried forward). To determine the predictors for therapy success receiver operating characteristics (ROC), curves were calculated using the 12-month data. TBF-12 total score, NRS loudness, and NRS annoyance were used as potential predictors and therapy success was defined as CGI-I7 ≤ 3.

The study was performed in accordance with good clinical practice guidelines and local ethics committees. All participating patients gave their written informed consent. Independent external clinical research associates and a clinical physician monitored the safety of the study. Data analysis was performed by an external contract research organization.

3. Results

189 patients finished the 12-month treatment and 11 patients dropped out for different reasons: eight stated nontreatment related reasons; two stated that their tinnitus did not change; and one stated that his tinnitus got louder.

The treatment was well tolerated and no serious adverse events (AE) were reported. An adverse event was defined as any untoward medical occurrence. Technical and handling problems were also documented as AE for this study. 89 product-related AEs were reported. Of these 89 product-related AEs, 40 were device related (i.e., technical and handling problems, rapidly solved). The other 49 AEs are considered to be therapy related. These were an additional atonal noise (15), additional tinnitus tone (3), increase in tinnitus burden (2), increase in loudness (13), tinnitus frequency shift (1), headaches (2), anxiety (1), tinnitus frequency increased to >10 kHz (2), discomfort (7), itching of ear canals (2), and otalgia (1). All adverse events were recorded as being temporary with no permanent or sustainable features.

After 12 months, TBF-12 (total score) showed a mean reduction of 4.1 points (−37.9%) compared to baseline ($P < 0.01$, df = 191, $t = -12.3$, Table 2, Figures 2(a) and 2(b)): mean TBF-12 score at baseline was 10.8 points and after 3 (6/12) months 7.9 (7.5/6.7) points. After 12 months, the number of patients within the TBF-12 categories *moderate* and *severe handicap* decreased from 33.8% to 13.9%, while the number of patients within the category *slight (no handicap)* increased from 31.8% to 64.1%. The TBF-12 based effect size of the treatment is 0.89, which corresponds to a large effect size.

Table 2: Results of TBF-12 and CGI-I7 scores.

(a)

Variable	Visit [month]	N	Mean	SD	Delta	P value
TBF-12 Score	0	195	10.8	5.0	n.a.	n.a.
	3	193	7.9	4.7	−27.3%	<0.01
	6	193	7.5	4.7	−30.8%	<0.01
	12	195	6.7	5.0	−37.9%	<0.01

(b)

CGI-I7 (after 12 months, $N = 196$)	Patients Number	Relative number	P value
Very much improved (1)	17	8.7%	
Much improved (2)	49	25%	
Slightly improved (3)	65	33.2%	
No change (4)	48	24.5%	<0.01
Slightly worse (5)	14	7.1%	
Much worse (6)	2	1%	
Very much worse (7)	1	0.5%	

At the visit after 12 months the results of CGI-I7 revealed that 131 (66.9%) patients reported an improvement of their tinnitus, that is, CGI-I7 categories 1, 2, or 3 ($P < 0.01$, $k = 131$, $N = 196$, Table 2, Figure 2(c)), 24.5% felt no change (category 4), and 8.6% reported feeling that their tinnitus had become worse (categories 5, 6, and 7) (Table 2). After 3 months of treatment 58.59% ($P < 0.01$, $k = 116$, $N = 198$) of the patients reported an improvement of their tinnitus.

After 12 months of treatment the loudness of tinnitus, as obtained by a numeric rating scale (0–100), was reduced by 11.1 points (18.9%) compared to baseline ($P < 0.01$, df = 194, $t = -4.53$, Table 3): mean NRS loudness at baseline was 58.6 points and after 3 (6/12) months 53.7 (51.0/47.5) points. Tinnitus related annoyance (also obtained by a numeric rating scale (0–100)) was reduced by 14.7 points (25.2%) after 12 months of treatment as compared to baseline ($P < 0.01$, df = 197, $t = -3,14$, Table 3). When asked if they are

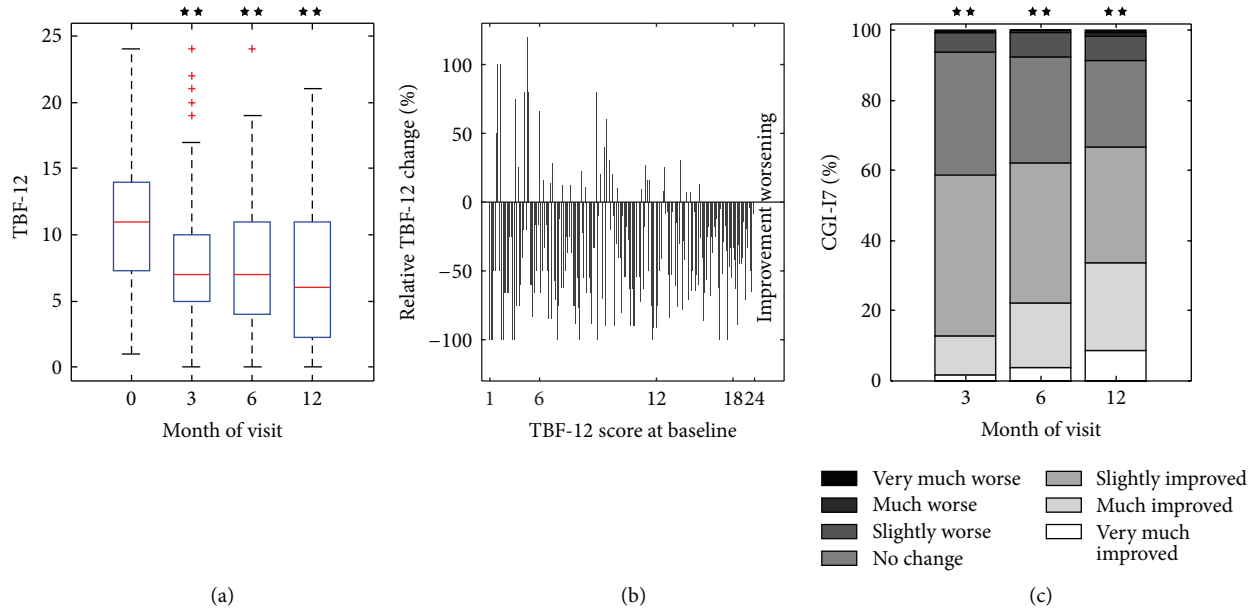


Figure 2: (a) TBF-12 scores at baseline and after 3, 6 and 12 months of treatment. (b) Relative TBF-12 change for the individual patients. The position of the bar on the x-axis indicates the TBF-12 score at baseline. (c) Distribution of the CGI-I7 scores after 3, 6 and 12 months of treatment. Stars indicate statistically significant results ($^{\star\star}P < 0.01$).

Table 3: NRS scales for loudness and annoyance.

Variable	Visit [month]	N	Mean	SD	Delta	P value
NRS loudness	0	197	58.6	21.9	n. a.	n. a.
	3	198	53.7	20.6	−8.4%	<0.05
	6	197	51.0	21.5	−13.0%	<0.01
	12	196	47.5	24.9	−18.9%	<0.01
NRS annoyance	0	198	58.3	25.2	n. a.	n. a.
	3	198	50.9	21.8	−12.7%	<0.01
	6	196	47.7	23.1	−18.2%	<0.01
	12	196	43.6	25.7	−25.2%	<0.01

free of tinnitus, after 12 months of treatment 54.4% of the patients reported either that they are tinnitus-free (4.1%) or that tinnitus has no negative influence on their life any more (50.3%).

In the course of the treatment the tinnitus pitch changed. In average a reduction of tinnitus pitch was observed (−11.2% after 3 months ($P < 0.05$, df = 361, $t = -2.44$) and −15.6% after 12 months of treatment ($P < 0.01$, df = 359, $t = -3.20$)). 55.6% of the patients showed a reduction of tinnitus frequency of more than 10%, 33.1% of the patient showed an increase of tinnitus frequency of more than 10%, and for the remaining 11.3% of patients the tinnitus frequency changed less than 10%. 80.0%/58.7% of patients with a reduction of tinnitus frequency >10% showed an improvement of TBF-12/NRS loudness, while this correlation is not significant (chi-squared test). These tinnitus pitch changes imply an adjustment of the therapy tones, which was done during the regular visits.

Based on the TBF-12 scores at baseline the patients were divided into four separate subgroups relating to tinnitus severity *slight (no handicap), mild, moderate*, and *severe*. At the end of the study, these scores were recorded as being reduced by 34.1%, 36.4%, 39.0%, and 41.5%, respectively, compared to the scores recorded at the beginning of therapy. The NRS loudness was reduced for these same subgroups by 20.7%, 17.2%, 17.6%, and 24.7% while the NRS annoyance was reduced by 18.5%, 21.9%, 32.2%, and 32.7%, respectively.

On average, the stimulation device was used by patients for five hours per day. Compliance was 87% at the beginning and fell to 73% after 12 months. "Compliance" was self-expressed by the patients and was defined as at least 4-hour daily stimulation. If the stimulation was split, then each stimulation block should be at least 1 hour long. We calculated receiver operating characteristics (ROC) curves to identify predictors for therapy success (therapy success was defined as CGI ≤ 3). Based on the 12-month data, the area under the curve (AUC) was as follows: TBF-12 total score: 0.73, NRS loudness: 0.82, and NRS annoyance: 0.83.

4. Discussion

This prospective, open-label, nonrandomized, noncontrolled multicenter clinical study with 200 chronic tinnitus patients demonstrates safety and good applicability, that is, good patient compliance and low drop-out rate, of acoustic CR Neuromodulation. 189 patients finished the 12-month treatment, which demonstrates a good patient adherence.

The applied treatment, acoustic CR neuromodulation, consists of a particular temporal pattern of stimulation tones intending the induction of local desynchronization of pathologically enhanced neuronal synchronization, which is

the neuronal correlate of the tinnitus symptoms. By inducing desynchronization, which also affects limbic structures associated with the emotional perception of tinnitus [8, 9, 14], the stimulation signals start the process of unlearning the pathological signal, with the aim of resulting in a long-term reduction of the tinnitus symptoms.

Analysis of the results of this multicenter clinical study demonstrates significant results in both primary endpoints. Both the TBF-12 and CGI-I7 results are statistically and clinically significant after 12 months of treatment [39]. The initial tinnitus severity had only moderate effects on the treatment effect. Furthermore, this study serves to demonstrate the safety of acoustic CR neuromodulation, since, of all device-related adverse events, none was serious (i.e., life threatening or caused a hospitalization of the patient or disablement, etc.).

The final results of the RRL study, including data from 200 patients, support the results of the original RESET study: similar results were obtained within the larger patient population under "real life" conditions. While in the RESET study after 3 months of treatment (group 1, same treatment as in RRL) a change of −28.8% was obtained for the tinnitus questionnaire (TQ), the current study revealed a change of −27.3% in TBF-12 scores after a similar duration (visit after 3 months) and −37.9% after 12 months. This indicates that a continuation of the treatment beyond the initial 3 months can be very beneficial for the patient. Continuous improvement over the whole duration of the study was also found for tinnitus loudness and annoyance and may suggest that a treatment duration beyond 12 months may further increase treatment efficacy.

The authors are aware of the limitations of this study, which has been designed as an open study without a control group. Thus, it is not possible to reach a final conclusion with regards to what extent the observed effects are unspecific and to what extent they actually represent the specific effects of CR neurostimulation. However, the ongoing improvement of patients over 12 months and their relatively high resistance to previous treatments make placebo effects highly unlikely. A spontaneous recovery is unlikely as well, given the relative long tinnitus duration of most patients. In 88.1% of the patients, a positive treatment effect over the first 3 months (i.e., CGI-I7 $\leq$ 3 at month 3) correlated with a positive treatment outcome after 12 months of therapy (i.e., CGI-I7 $\leq$ 3 at month 12). 58.6% of the patients recorded a positive effect after 3 months of treatment and 66.5% after 12 months. TBF-12 improvement was seen to augment in this CGI-I7-based responder population from −31.9% (3 months) to −50.8% (12 months), NRS annoyance changed by −21.6% (3 months) and −35.6% (12 months), and NRS loudness changed by −16.7% (3 months) and −31.7% (12 months), while the CGI-I7-based nonresponders showed only moderate changes (TBF-12: −21.3% and −20.6%, NRS annoyance: +0.1% and −5.4%, and NRS loudness: +3.9% and −0.3% at 3 months and at 12 months, resp.). NRS annoyance resulted in the highest value in the ROC test, which indicates that it is a good metric for therapy success. Therefore, CGI-I7 combined with TBF-12 and NRS annoyance seems to be a reliable and easy to handle set of questionnaires and metrics, which can be used in ENT outpatient settings as indicators of treatment effects.

Our data (−37.9% mean change in TBF-12) can be compared with recent results on effects of standard tinnitus care and cognitive behavior therapy (CBT) [40]. Standard care (hearing aid or tinnitus masker, $n = 161$, 8-month treatment) resulted in a change of tinnitus handicap inventory (THI) and tinnitus questionnaire (TQ) by −11.9% and −13.3%, respectively, while specialized care (CBT, $n = 175$, 8 months treatment) resulted in a change of THI and TQ by −26.5% and −26.2%, respectively.

Thus, in summary, the RRL study reveals that acoustic CR neuromodulation, when applied for 12 months and used 4–6 hours per day in patients suffering from primary and tonal or tone-like tinnitus, is a safe and feasible technique and exerts encouraging effects on tinnitus loudness and severity.

Conflict of Interests

Christian Hauptmann is employed by Jülich Research Center, formerly working with ANM GmbH (Cologne, Germany). He works as consultant for Brook Henderson Group and has received research funding from the European Community, the Federal Ministry of Education and Research (Germany), the Deutsche Forschungsgemeinschaft, and the Helmholtz Association. Armin Ströbel is employed by CERES GmbH and worked as statistician of the CRO during the RRL study. He was responsible for the statistical analysis of the trail data. Mark Williams has a contractual relationship with The Tinnitus Clinic Ltd. The Tinnitus Clinic Ltd. is the UK distributer for the acoustic coordinated reset neuromodulation therapy device. Nitesh Patel has no financial interests to declare. Hannes Wurzer works as consultant of Brook Henderson Group. Tatjana von Stackelberg has no financial interests to declare. Uwe Brinkmann has no financial interests to declare. Berthold Langguth received honoraria and speakers' fee from ANM, Astra Zeneca, Autifony, Lundbeck, Merz, MagVenture, Novartis, Pfizer, and Servier, research funding from the Tinnitus Research Initiative, the German Research Foundation, the German Bundesministerium für Bildung und Forschung, the American Tinnitus Association, AstraZeneca, and Cerbomed, funding for equipment from MagVenture, and travel and accommodation payments from Medtronic, Lilly, Servier, and Pfizer. Peter A. Tass is employed by Jülich Research Center and works as Consulting Professor at Stanford University, formerly (till 07/2013) working with ANM GmbH (Cologne, Germany) and shareholder of ANM. He has received research funding from the European Community, the Federal Ministry of Education and Research (Germany), the Deutsche Forschungsgemeinschaft, the Helmholtz Association, Biomedical Primate, and the Michael J Fox Foundation. The clinical trial RRL was financially supported by ANM GmbH, Germany, and Brook Henderson Group, UK. Patents protect acoustic CR neuromodulation, for example, US patent 8,423,144, device and method for auditory stimulation. Peter A. Tass is an inventor of this patent, and the assignee is Jülich Research Center.

Acknowledgments

The authors are very grateful for the contribution of the 23 ENT's that treated the 200 patients. Namely, this is the alphabetic order: Krister Björn Martin Bergmann (Nürtingen), Andreas Bodlien (Braunschweig), Uwe Brinkmann (Oelde), Christiane Fleissner (Freiburg), Joachim Gubitz (Köln), Beatrix Hahlbrock (Koblenz), Ute Hegemann-Gärtner (Grevenbroich), Kai Helling (Mainz), Mathias Joachim Hügelschäffer (Philippsburg), Ovidiu König (Berlin), Jan Löhler (Bad Bramstedt), Olaf Müller (Augsburg), Daniel Osterland (Berlin), Tatjana von Stackelberg (Meerbusch), Kathrin Stölzer (Halle/Saale), Axel Rösler (Radevormwald), Hans-Günther Ullmann (Melsungen), Tobias-Sebastian Waller (Schweinfurt), Joachim Wichmann (Krefeld), Stephan Wolf (Fürth), Hannes Wurzer (München), Peter Ziegelmüller (Mannheim), and Marcus Zwingmann (Frankfurt). They also want to thank Christine Droll-Popilar and Violetta Pithan for data entry and monitoring, respectively.

References

[1] J. J. Eggermont and L. E. Roberts, "The neuroscience of tinnitus," *Trends in Neurosciences*, vol. 27, no. 11, pp. 676–682, 2004.

[2] A. Axelsson and A. Ringdahl, "Tinnitus—a study of its prevalence and characteristics," *British Journal of Audiology*, vol. 23, no. 1, pp. 53–62, 1989.

[3] B. Langguth, "Tinnitus: the end of therapeutic nihilism," *The Lancet*, vol. 379, no. 9830, pp. 1926–1928, 2012.

[4] N. Weisz, S. Moratti, M. Meinzer, K. Dohrmann, and T. Elbert, "Tinnitus perception and distress is related to abnormal spontaneous brain activity as measured by magnetoencephalography," *PLoS Medicine*, vol. 2, no. 6, article e153, 2005.

[5] K. Dohrmann, T. Elbert, W. Schlee, and N. Weisz, "Tuning the tinnitus percept by modification of synchronous brain activity," *Restorative Neurology and Neuroscience*, vol. 25, no. 3-4, pp. 371–378, 2007.

[6] N. Kahlbrock and N. Weisz, "Transient reduction of tinnitus intensity is marked by concomitant reductions of delta band power," *BMC Biology*, vol. 6, article 4, 2008.

[7] M. Ortmann, N. Müller, W. Schlee, and N. Weisz, "Rapid increases of gamma power in the auditory cortex following noise trauma in humans," *European Journal of Neuroscience*, vol. 33, no. 3, pp. 568–575, 2011.

[8] P. A. Tass, I. Adamchic, H. J. Freund, T. von Stackelberg, and C. Hauptmann, "Counteracting tinnitus by acoustic coordinated reset neuromodulation," *Restorative Neurology and Neuroscience*, vol. 30, no. 2, pp. 137–159, 2012.

[9] I. Adamchic, T. Toth, C. Hauptmann, and P. A. Tass, "Reversing pathologically increased EEG power by acoustic coordinated reset neuromodulation," *Human Brain Mapping*, vol. 35, no. 5, pp. 2099–2118, 2014.

[10] J. J. Eggermont and P. A. Tass, "Maladaptive neural synchrony in tinnitus: origin and restoration," *Frontiers in Neurology*. In press.

[11] W. Schlee, N. Weisz, O. Bertrand, T. Hartmann, and T. Elbert, "Using auditory steady state responses to outline the functional connectivity in the tinnitus brain," *PLoS ONE*, vol. 3, no. 11, Article ID e3720, 2008.

[12] W. Schlee, T. Hartmann, B. Langguth, and N. Weisz, "Abnormal resting-state cortical coupling in chronic tinnitus," *BMC Neuroscience*, vol. 10, article 11, 2009.

[13] D. De Ridder, A. B. Elgoyhen, R. Romo, and B. Langguth, "Phantom percepts: tinnitus and pain as persisting aversive memory networks," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 108, no. 20, pp. 8075–8080, 2011.

[14] A. N. Silchenko, I. Adamchic, C. Hauptmann, and P. A. Tass, "Impact of acoustic coordinated reset neuromodulation on effective connectivity in a neural network of phantom sound," *NeuroImage*, vol. 77, pp. 133–147, 2013.

[15] P. Adjamian, M. Sereda, O. Zobay, D. A. Hall, and A. R. Palmer, "Neuromagnetic indicators of tinnitus and tinnitus masking in patients with and without hearing loss," *Journal of the Association for Research in Otolaryngology*, vol. 13, no. 5, pp. 715–731, 2012.

[16] R. Llinás, F. J. Urbano, E. Leznik, R. R. Ramírez, and H. J. F. Van Marle, "Rhythmic and dysrhythmic thalamocortical dynamics: GABA systems and the edge effect," *Trends in Neurosciences*, vol. 28, no. 6, pp. 325–333, 2005.

[17] D. E. Tunkel, C. A. Bauer, and G. H. Sun, "Clinical practice guideline: tinnitus," *Otolaryngology—Head and Neck Surgery*, vol. 151, no. 2, supplement, pp. S1–S40, 2014.

[18] P. Martinez-Devesa, A. Waddell, R. Perera, and M. Theodoulou, "Cognitive behavioural therapy for tinnitus," *Cochrane Database of Systematic Reviews*, no. 8, Article ID CD005233, 2010.

[19] D. J. Hoare, M. Edmondson-Jones, M. Sereda, M. A. Akeroyd, and D. Hall, "Amplification with hearing aids for patients with tinnitus and co-existing hearing loss," *The Cochrane Database of Systematic Reviews*, vol. 1, Article ID CD010151, 2014.

[20] J. Hobson, E. Chisholm, and A. El Refaie, "Sound therapy (masking) in the management of tinnitus in adults," *Cochrane Database of Systematic Reviews*, no. 11, Article ID CD006371, 2012.

[21] J. S. Phillips and D. McFerran, "Tinnitus retraining therapy (TRT) for tinnitus," *Cochrane Database of Systematic Reviews*, vol. 3, Article ID CD007330, 2010.

[22] M. P. Hilton, E. F. Zimmermann, and W. T. Hunt, "Ginkgo biloba for tinnitus," *The Cochrane Database of Systematic Reviews*, vol. 3, Article ID CD003852, 2013.

[23] P. Baldo, C. Doree, P. Molin, D. McFerran, and S. Cecco, "Antidepressants for patients with tinnitus," *Cochrane Database of Systematic Reviews*, vol. 9, Article ID CD003853, 2012.

[24] C. E. Hoekstra, S. P. Rynja, G. A. van Zanten, and M. M. Rovers, "Anticonvulsants for tinnitus," *Cochrane Database of Systematic Reviews*, no. 7, Article ID CD007960, 2011.

[25] M. H. Bennett, T. Kertesz, M. Perleth, P. Yeung, and J. P. Lehm, "Hyperbaric oxygen for idiopathic sudden sensorineural hearing loss and tinnitus," *Cochrane Database of Systematic Reviews*, vol. 10, Article ID CD004739, 2012.

[26] J. I. Kim, J. Y. Choi, D. H. Lee, T. Y. Choi, M. S. Lee, and E. Ernst, "Acupuncture for the treatment of tinnitus: a systematic review of randomized clinical trials," *BMC Complementary and Alternative Medicine*, vol. 12, article 97, 2012.

[27] B. Langguth and D. de Ridder, "Tinnitus: therapeutic use of superficial brain stimulation," *Handbook of Clinical Neurology*, vol. 116, pp. 441–467, 2013.

[28] P. A. Tass, "A model of desynchronizing deep brain stimulation with a demand-controlled coordinated reset of neural subpopulations," *Biological Cybernetics*, vol. 89, no. 2, pp. 81–88, 2003.

[29] P. A. Tass and M. Majtanik, "Long-term anti-kindling effects of desynchronizing brain stimulation: a theoretical study," *Biological Cybernetics*, vol. 94, no. 1, pp. 58–66, 2006.

[30] P. A. Tass and O. V. Popovych, "Unlearning tinnitus-related cerebral synchrony with acoustic coordinated reset stimulation: theoretical concept and modelling," *Biological Cybernetics*, vol. 106, no. 1, pp. 27–36, 2012.

[31] I. Adamchic, B. Langguth, C. Hauptmann, and P. A. Tass, "Abnormal brain activity and cross-frequency coupling in the tinnitus network," *Frontiers in Neuroscience*, vol. 8, article 284, 2014.

[32] I. Adamchic, B. Langguth, C. Hauptmann, and P. A. Tass, "Psychometric evaluation of visual analog scale for the assessment of chronic tinnitus," *The American Journal of Audiology*, vol. 21, no. 2, pp. 215–225, 2012.

[33] I. Adamchic, P. A. Tass, B. Langguth et al., "Linking the tinnitus questionnaire and the subjective clinical global impression: which differences are clinically important?" *Health and Quality of Life Outcomes*, vol. 10, article 79, 2012.

[34] R. Görtelmeyer, J. Schmidt, M. Suckfüll et al., "Assessment of tinnitus-related impairments and disabilities using the German THI-12: sensitivity and stability of the scale over time," *International Journal of Audiology*, vol. 50, no. 8, pp. 523–529, 2011.

[35] B. Langguth, R. Goodey, A. Azevedo et al., "Consensus for tinnitus patient assessment and treatment outcome measurement: tinnitus Research Initiative meeting, Regensburg, July 2006," *Progress in Brain Research*, vol. 166, pp. 525–536, 2007.

[36] P. M. Kreuzer, M. Landgrebe, V. Vielsmeier, T. Kleinjung, D. de Ridder, and B. Langguth, "Trauma-associated tinnitus," *Journal of Head Trauma Rehabilitation*, vol. 29, no. 5, pp. 432–442, 2014.

[37] B. Lysyansky, O. V. Popovych, and P. A. Tass, "Desynchronizing anti-resonance effect of m: N ON–OFF coordinated reset stimulation," *Journal of Neural Engineering*, vol. 8, no. 3, Article ID 036019, 2011.

[38] U. S. Bankstahl, E. P. Elkin, A. Gebauer, and R. Görtelmeyer, "Validation of the THI-12 questionnaire for international use in assessing tinnitus: A multi-centre, prospective, observational study," *International Journal of Audiology*, vol. 51, no. 9, pp. 671–677, 2012.

[39] F. Zeman, M. Koller, M. Schecklmann et al., "Tinnitus assessment by means of standardized self-report questionnaires: psychometric properties of the Tinnitus Questionnaire (TQ), the Tinnitus Handicap Inventory (THI), and their short versions in an international and multi-lingual sample," *Health and Quality of Life Outcomes*, vol. 10, article 128, 2012.

[40] R. F. F. Cima, I. H. Maes, M. A. Joore et al., "Specialised treatment based on cognitive behaviour therapy versus usual care for tinnitus: a randomised controlled trial," *The Lancet*, vol. 379, no. 9830, pp. 1951–1959, 2012.

Hindawi Publishing Corporation
BioMed Research International
Volume 2015, Article ID 290425, 12 pages
http://dx.doi.org/10.1155/2015/290425

Research Article

Hyperacusis Questionnaire as a Tool for Measuring Hypersensitivity to Sound in a Tinnitus Research Population

Kathryn Fackrell,[1,2] Constance Fearnley,[3] Derek J. Hoare,[1,2] and Magdalena Sereda[1,2]

[1]*NIHR Nottingham Hearing Biomedical Research Unit, Nottingham NG1 5DU, UK*
[2]*Otology and Hearing Group, Division of Clinical Neuroscience, School of Medicine, University of Nottingham, Nottingham NG7 2RD, UK*
[3]*School of Medicine, University of Nottingham, Nottingham NG7 2RD, UK*

Correspondence should be addressed to Magdalena Sereda; magdalena.sereda@nottingham.ac.uk

Received 17 April 2015; Revised 17 June 2015; Accepted 15 July 2015

Academic Editor: Tobias Kleinjung

Hypersensitivity to external sounds is often comorbid with tinnitus and may be significant for adherence to certain types of tinnitus management. Therefore, a clear measure of sensitivity to sound is important. The aim of this study was to evaluate the validity and reliability of the Hyperacusis Questionnaire (HQ) for use as a measurement tool using data from a sample of 264 adults who took part in tinnitus research. We evaluated the HQ factor structure, internal consistency, convergent and discriminant validity, and floor and ceiling effects. Internal consistency was high (Cronbach's alpha = 0.88) and moderate correlations were observed between the HQ, uncomfortable loudness levels, and other health questionnaires. Confirmatory factor analysis revealed that the original HQ three-factor solution and a one-factor solution were both a poor fit to the data. Four problematic items were removed and exploratory factor analysis identified a two-factor (attentional and social) solution. The original three-factor structure of the HQ was not confirmed. All fourteen items do not accurately assess hypersensitivity to sound in a tinnitus population. We propose a 10-item (2-factor) version of the HQ, which will need to be confirmed using a new tinnitus and perhaps nontinnitus population.

1. Introduction

Hyperacusis is most commonly defined as increased sensitivity to ordinary environmental sounds that would not usually be bothersome to most individuals [1–3]. Hyperacusis is a broad spectrum condition affecting individuals to various degrees. The main difference between hypersensitivity to sound and conditions such as phonophobia (fear of sound) and misophonia (dislike of sound) is that the latter two usually involve an emotional response to specific sounds [4]. Loudness recruitment (abnormal growth in the perception of loudness) may be a distinct condition or can accompany hyperacusis in people with cochlear hearing loss. Baguley [5] suggested that loudness recruitment can be distinguished from hypersensitivity to sound based on the intensity of the sounds perceived as uncommonly loud (moderate intensity in the case of loudness recruitment and low intensity in the case of hyperacusis). He also notes that loudness recruitment, unlike hyperacusis, does not vary with mood.

Prevalence of hypersensitivity to sound in adults is estimated at 8 or 15% [6, 7]. It can influence emotional well-being, hearing, sleep, and concentration, cause anxiety, and interfere with speech perception in noise [8, 9]. It is estimated that about half of patients with hyperacusis also have a psychiatric or anxiety disorder [10]. Among the possible etiologies of hyperacusis are conditions involving the peripheral auditory system (e.g., Bell's palsy, Ramsay Hunt syndrome, noise-induced hearing loss, Ménière's disease), diseases and syndromes of central nervous system (e.g., headaches, depression, head injury, Williams's syndrome, learning disabilities, spinal problems), and hormonal (e.g., Addison's disease) and infectious diseases (e.g., lyme disease). However, in most cases hypersensitivity to sound has no known cause [3].

Hypersensitivity to sound and tinnitus (perception of sound or noise in the absence of any external acoustic stimulation [11]) are often comorbid. The prevalence of tinnitus among people with hypersensitivity to sound is much higher than in the general population and with estimates of 40% [12], 79% [10], and 86% [13]. Similar to tinnitus, there are several potential pathophysiological mechanisms that might lead to hypersensitivity to sound and similar to tinnitus those mechanisms are not mutually exclusive. Increased prevalence of hypersensitivity to sound in a number of conditions points to 5-hydroxytryptamine (5-HT) dysfunction as one likely mechanism [3, 14]. Interestingly a link between tinnitus and 5-HT dysfunction has also been proposed [3]. One of the postulated functions of 5-HT in the auditory system is modulating central gain [15].

Jastreboff and Hazell [16] described hypersensitivity to sound as a pretinnitus state as it often occurs before the onset of tinnitus. They postulated that hypersensitivity to sound is an effect of an increased gain in the central auditory system. Increased central gain has also been postulated as one of the possible mechanisms of tinnitus generation [17, 18]. Association between hypersensitivity to sound, tinnitus, and peripheral auditory system damage present in stapedectomy, Menieres's disease, and sensorineural hearing loss led to hypotheses assuming peripheral contribution to the generation of hypersensitivity to sound [14].

The strong association between hypersensitivity to sound and tinnitus may have serious implications for research and management of both conditions. Both may have a significant influence on patterns of auditory activity in response to external sounds. The importance of controlling for hypersensitivity to sound in neuroimaging studies of tinnitus has been highlighted in a study by Gu et al. [19] who demonstrated that the increase in neuronal excitability to sounds in tinnitus patients (previously associated with tinnitus) may be ascribed to hypersensitivity to sound rather than to a mechanism specifically related to tinnitus. Several studies point to an association between tinnitus annoyance and the presence of hypersensitivity to sound [20, 21] where tinnitus annoyance is higher in patients with comorbid hypersensitivity to sound. The presence of hypersensitivity to sound can also influence the acceptability and adherence to certain tinnitus management options such as sound therapy. Therefore, a reliable measure of hypersensitivity to sound is important for tinnitus management.

There is no standard protocol for evaluating hypersensitivity to sound. The most common approach includes history taking and measuring uncomfortable loudness levels (ULLs) as a first step in the diagnosis [22]. In people with hypersensitivity to sound ULLs are usually lower than average over all or specific frequencies in both or one ear [5]. According to P. J. Jastreboff and M. M. Jastreboff [22], the average ULLs for patients reporting problems with sound tolerance are between 60 and 85 dB HL, whilst for all other patients ~100 dB HL. ULLs of 70 dB HL or less were suggested by Anari and colleagues as a criterion for diagnosis of hypersensitivity to sound [13, 23]. One common problem with measuring ULLs is high variability and strong dependence of the results on the instruction given. Studies that used different instructions found that the difference in ULLs ranged from 23 to 27 dB HL depending on the frequency [24, 25]. For instance, Dawson Jr. [24] found that, in people with normal hearing and no complaint of hypersensitivity to sound, ULLs were as low as 68 dB HL for 250 Hz, which will be diagnosed as hypersensitivity to sound according to the definition of Anari and colleagues [13]. Test-retest reliability of ULLs has been questioned [26]. Therefore, evidence for the utility of ULLs is mixed.

Patient-reported outcome measures (questionnaires) are used to measure hypersensitivity to sound specific health related quality of life and to diagnose hyperacusis. A small number of questionnaires have been developed to date, including the German Questionnaire on Hypersensitivity to Sound (G Ü F [27]; German version validated in tinnitus patients by Bläsing et al. [28]). The G Ü F assesses the subjective distress associated with hypersensitivity to sound which was considered a better indicator of treatment needs than audiological findings [28]. The German version of the questionnaire has been used in research [29]. Although the English translation of the questionnaire is available, this version has not been validated and has not been used in the clinics or research. The Multiple-Activity Scale for Hyperacusis (MASH) [30] is an interview-based questionnaire which assesses level of annoyance in relation to hypersensitivity to sound. Finally, the Hyperacusis Questionnaire (HQ) [31] was developed and a French version was validated using a general population who did not necessarily complain of sensitivity to sound. During development of the HQ normative data were used to estimate that a score greater than 28 was significantly different to the population total mean score of 15 points and so this was taken to represent "strong auditory hypersensitivity" (hyperacusis) (maximum possible score = 42) [31]. Using exploratory factor analysis, three factors were identified for the HQ (attentional, social, and emotional), but together they only accounted for 48% of the variance; that is, there was a lot of unexplained variance and likely measurement error [32]. Factor loadings were all above 0.3. Minor cross loading in particular in the social factor leads us to question the uniqueness of the subscales. Meeus and colleagues [33] performed validation of a Dutch version of the questionnaire and identified four subscales using exploratory factor analysis. This further calls into question the reliability of the original questionnaire structure identified by Khalfa and colleagues [31]. Exploratory factor analysis is recommended during the development of questionnaires as it explores all possible interrelationships between the set of observed variables without postulating a theoretical structure. However, confirmatory factor analysis is necessary to assess a premediated structure based on theory or/and exploratory factor analysis findings [34, 35]. To date the psychometric properties, in particular the original structure of the HQ, have not been confirmed or assessed in a UK population; no confirmatory factor analysis has been conducted. Yet, the questionnaire is used in tinnitus research studies as a screening tool for exclusion of participants with hyperacusis [36–39] and as an outcome measure of treatment-related change [10, 33], although it was not designed with this purpose in mind [31].

Table 1: Descriptive statistics for the study measures.

Questionnaire/subscale	Number of items	Total range	Descriptive statistics		Reliability		
			Mean	SD	Range	α	N
Hyperacusis Questionnaire [31]	14	0–42	14.9	8.0	0–37	0.88	264
Attentional	4	0–12	4.0	2.7	0–10	0.71	
Social	6	0–18	6.1	3.7	0–18	0.75	
Emotional	4	0–12	4.7	3.0	0–12	0.77	
Tinnitus Handicap Inventory (THI) [46]	25	0–100	35.0	21.6	0–94		115
Tinnitus Handicap Questionnaire (THQ) [45]	27	0–100	37.9	17.6	5.6–88.9		195
Beck's Depression Inventory-II (BDI-II) [47]	21	0–63	7.9	7.2	0–30		54
Beck's Depression Inventory-Fast Screen (BDI-FS) [49]	7	0–21	2.0	2.7	0–14		142
Beck's Anxiety Inventory (BAI) [48, 55]	21	0–63	7.0	6.9	0–43		200
Uncomfortable loudness levels at 1 kHz (dB HL)	—	—	87.8	14.3	60–120		40

The maximum score is 42 for the HQ, 100 for THI and THQ, 63 for BDI and BAI, and 21 for the BDI-FS. The reliability alpha (α) is presented for the HQ total and subscale scores. N = effective samples.

The aim of this study was to empirically evaluate the validity and reliability of the HQ for use as measurement tool in a specific population, that is, adults taking part in tinnitus research. The psychometric validation reported here focuses on evaluating the original three-factor structure of the HQ, particularly item identification with the three factors and the relationship between the three factors and the overall hypersensitivity to sound construct (score), and the reliability (internal consistency), validity (discriminant validity), and responsiveness (floor and ceiling effects) of the HQ using a large UK population of research participants with tinnitus.

2. Materials and Methods

2.1. Participants and Procedures. The study was a retrospective analysis of data collected during a series of tinnitus research studies conducted at the NIHR Nottingham Hearing Biomedical Research Unit and MRC Institute of Hearing Research between 2008 and 2014. Studies included randomised controlled trials (RCTs) [40, 41], clinical cohort studies [42, 43], an imaging study using magnetoencephalography [38, 39], and a feasibility study [44]. In those studies the HQ was used either as a screening tool for exclusion of participants with hyperacusis [39–41, 43] or for classification of participants [38]. Additional assessments included the Tinnitus Handicap Questionnaire (THQ) [45]; Tinnitus Handicap Inventory (THI) [46]; Beck's Depression Inventory-II (BDI-II) [47]; Beck's Anxiety Inventory (BAI) [48]; Beck's Depression Inventory-Fast Screen (BDI-FS) [49]; uncomfortable loudness levels (ULLs). In some cases participants had completed the eligibility assessments for more than one study; to prevent an overlap in the data, for these participants only one set of questionnaire data was used. In these cases, the most complete dataset was chosen. In total, 264 people with tinnitus (158 male, 106 female) with an average age of 58.7 years (range: 24 to 85 years) completed the HQ and some or most of the assessment questionnaires. Forty people completed ULL assessment.

2.2. Missing Data. Only participants who completed the HQ were included (n = 264). Due to variability in the eligibility assessments or because of participants being withdrawn at different points in their assessment, not all 264 participants complete all of the other assessments. For the convergent and discriminant validity therefore, we conducted pairwise deletion to enable the use of most data; the effective samples for each comparison are provided in Table 1.

2.3. Measures

2.3.1. Hyperacusis Questionnaire (HQ). The HQ is a two-part questionnaire. The first part consists of binary questions which aim to gather general information of auditory disorders and noise exposure, whilst the second part consists of 14 negatively worded items, which are rated on a 4-point scale: "no" (0 points), "yes, a little" (1 point), "yes, quite a lot" (2 points), and "yes, a lot" (3 points). The total provides the measure of hypersensitivity to sound with higher scores indicating greater sensitivity. The mean global score ranges from 0 to 42 and a global score >28 indicates hyperacusis [31]. Items related to the three subscales can also be summed to provide subscale scores.

2.3.2. Tinnitus Handicap Inventory (THI). The THI quantifies the impact of tinnitus on daily living [46, 50]. For instance, item 1 asks "Because of your tinnitus is it difficult for you to concentrate?". Each of 25 items is rated on a 3-point scale: "yes" (4 points), "sometimes" (2 points), and "no" (0 points). The mean global score reflects the sum of all responses with a global score of 100 indicating greatest impact on everyday function. Scores are interpreted using the following categories: slight problem (0–16), mild (18–36), moderate (38–56), severe (58–76), and catastrophic (78–100) [51]. Newman et al. [46] described three subscales measuring functional, emotional, and catastrophic impact of tinnitus. However, the reliability of these subscales has been questioned [52].

2.3.3. Tinnitus Handicap Questionnaire (THQ). The THQ measures the perceived degree of handicap associated with tinnitus [45]. For example, item 1 asks "I have support from my friends regarding my tinnitus." For each of 27 items, participants assign a number between 0 (strongly disagree) and 100 (strongly agree) to indicate their agreement. All items are negative descriptors with the exception of two items which are reverse-scored before all the responses are summed and weighted to give a global score out of 100. Kuk et al. [45] identified three subscales ((1) physical, emotional, and social effects; (2) hearing and communication ability; (3) individual's perception of tinnitus) but only subscales 1 and 2 were found to be reliable [45].

2.3.4. Beck's Depression Inventory-II (BDI-II). The BDI-II measures severity of depressive symptoms [47, 53, 54]. For each of 21 items, participants select one of four statements (scoring 0–3 points) according to how they have felt over the previous two weeks. For example, item 1 measures sadness: (0) "I do not feel sad"; (1) "I feel sad much of the time"; (2) "I am sad all the time"; (3) "I am so sad or unhappy that I cannot stand it." Higher scores indicate increased levels of depressive symptomatology. Responses are summed to form a global score out of 63, with a score of 31–40 categorised as "severe depression" and a score of over 40 as "extreme depression" [47].

2.3.5. Beck's Depression Inventory-Fast Screen (BDI-FS). The BDI-FS is a quicker quantitative screen for depression than the BDI, which excludes symptoms possibly related to other medical conditions [49]. Each of the 7 items is rated on a 4-point scale (scoring 0–3 points) with four descriptor statements. Responses are summed to form a global score out of 21, with a higher score indicating a higher level of depression.

2.3.6. Beck's Anxiety Inventory (BAI). The BAI measures 21 common symptoms of clinical anxiety [48, 55, 56]. Participants indicate the degree to which the particular symptom has bothered them over the previous week by selecting one of four response options (0 to 3). For example, item 1 measures numbness or tingling: (0) "Not at all"; (1) "Mildly; it did not bother me much"; (2) "Moderately; it was very unpleasant, but I could stand it"; (3) "Severely; I could barely stand it." Again responses are summed to give a global score out of 63. Scores of 0–21 indicate very low anxiety and scores exceeding 36 indicate cause for concern [48, 55].

2.3.7. Uncomfortable Loudness Levels (ULLs). The ULLs of 40 participants were measured across two of the included studies [38, 39]. ULLs were tested using a 1 kHz pure tone delivered to each ear using an audiometer. Tones were presented for 1 second with 1 second quiet periods and increased in 5 dB steps until the participant responded that the sound had reached an uncomfortable level. All participants had normal hearing thresholds at 1 kHz. ULLs were conducted for both ears and averaged to give a mean ULL value at 1 kHz for each individual.

2.4. Statistical Analysis

2.4.1. Factor Structure: Confirmatory Factor Analysis. Confirmatory factor analysis (CFA) was conducted on HQ data from 264 patients with tinnitus to test the fit of the 3-factor structure devised by Khalfa et al. (Figure 1) [31]. Following this, to evaluate a modified version of the HQ, the full dataset (N: 264) was randomly split into two similar sized independent groups: sample A (50% N: 132) and sample B (50% N: 132). CFA was conducted on the data from sample A to test the fit of a one-factor structure. Data from sample B were used for exploratory factor analysis (method below). CFA models were specified and estimated using Mplus version 7 [57].

The 3-factor model included (i) one second-order factor consistent with the global measure of "hypersensitivity to sound" (variance fixed at 1) and three first-order factors corresponding to the three HQ subscales (attentional, social, and emotional), (ii) fourteen observed variables, each freely estimated on their designated factor with zero loadings on the other factors with error variance assumed to be uncorrelated and random (constrained to zero).

The one-factor model was specified to include one general factor corresponding to hypersensitivity to sound, with fourteen observed variables corresponding to the 14 items of the HQ and uniqueness variance associated with each item.

All 14 items of the HQ were rated using polytomous scale. The data were modelled accordingly as categorical variables using the robust weighted least squares estimator (WLSMV) in Mplus [57]. Compared to other methods such as maximum likelihood (ML) and weighted least squares (WLS), WLSMV produces robust estimations, in particular robust standard error and adjusted Chi-square test statistics (χ^2) for categorical data with small sample sizes and non-normality in the data [58, 59]. In this study since all variables are categorical, WLSMV is estimated using polychoric correlation matrix of the underlying continuous response variables. These latent responses are related to the threshold parameters of the observed categorical variables, in which the thresholds reflect the position on the underlying continuous and normally distributed characteristic that distinguishes the categories of the observed polytomous variable [58]. The factor intercorrelations were initially examined to access the degree in which the factor relates to one another and overlaps in content before the model as a whole was evaluated (the second-order component of the model). Highly correlated factors (>0.85) are evidence of poor distinction between constructs (poor discriminant validity). Weakly correlated factors (<0.30) indicate unrelated content that is potentially measuring an alternative underlying construct [58, 60].

The goodness of fit was determined using WLSMV χ^2 [61], Comparative Fit Index (CFI) [62], Tucker-Lewis Index (TLI) [63], and weighted root-mean-square residual (WRMR) [57]. An indication of good model fit is a small nonsignificant χ^2 estimate ($p < 0.05$) that relative to the degrees of freedom is ≤2.0, CFI and TLI estimates that exceed 0.90 (preferably exceeding 0.95) [64], and WRMR values below 0.95. Root Mean Square Error of Approximation (RMSEA) [65] and confidence intervals (CIs) were reported

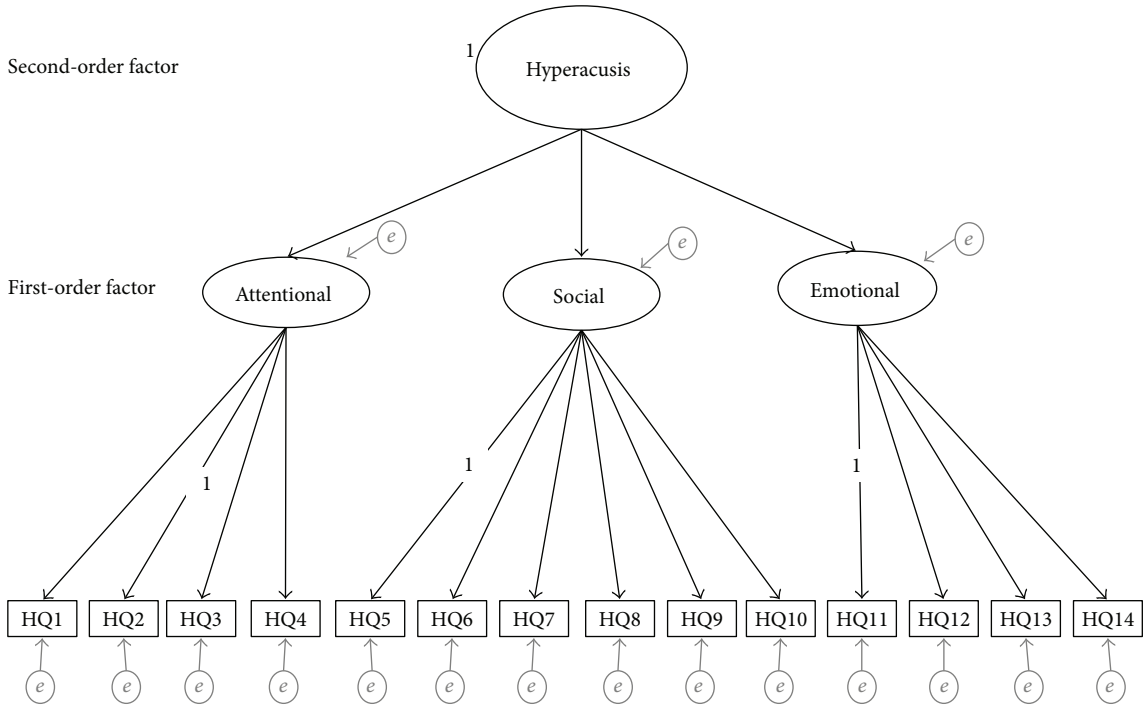


Figure 1: Theoretical 3-factor structure of the Hyperacusis Questionnaire (HQ). The model represents the proposed relationships between the items (observed variables), the first-order factors consistent with attentional, social, and emotional subscales, and the second-order factor consistent with the global measure of "hypersensitivity to sound" (variance fixed at 1). Variance fixed at 1 for second-order factor and items 2, 5, and 11. The unidirectional black arrows represent the direct effects of the second-order factor onto the three first-order factors and the direct effects of the first-order factors onto the observed variables. The fourteen observed variables are represented as HQ1 to HQ14, with all items only associated with their designated factor. The unidirectional grey arrows represent the error variance (e) associated with each variable, each freely estimated on their designated factor with zero loadings on the other factors with error variance assumed to be uncorrelated and random (constrained to zero). e = residual variance (error and uniqueness terms).

with values of less than 0.05 and CIs within 0.08 indicating acceptable fit [58, 64, 66, 67]. These cut-off points serve as guidelines for acceptable fit for the model that should be evaluated alongside the other CFA findings, that is, the factor loadings [67].

To compare the one and three factor models, the correct χ^2 difference tests for nested models were assessed using the DIFFTEST command in Mplus [57, 58].

Squared standardised factor loadings provide the basis for interpretation of the factor loading estimates with categorical data. Squared standardised factor loadings (and standardised factor loadings) were therefore examined to evaluate the amount of variance in the underlying continuous response variable explained by the latent constructs (first-order and second-order factors). The strength of these loadings is relative to the amount of variance by the model; therefore, the higher the loading value, the less the error associated with the model and the better the fit. Alternatively, low loadings (<0.4) indicate measurement error and are a potential source of poor model fit [34, 60]. Modification Index (MI) was used to identify any misspecification in the parameters of the model, with values exceeding 10 indicating a source of poor model fit [60]. The Expected Parameter Change (EPC) value was used to identify the magnitude of improvement to model fit if the parameters were freely estimated in a subsequent analysis. Together, these were only used to identify which parameters could be adjusted if they significantly improved model fit and were supported by conceptual foundations [60, 68].

2.4.2. Factor Structure: Exploratory Factor Analysis. Data from sample B were modelled in exploratory factor analysis using the WLSMV estimator and oblique rotations [58, 69]. Following the Kaiser criteria, factors with eigenvalues above 1 were extracted [70]. The scree plot was also examined to confirm factor extraction. Communalities were assessed for each item with communalities below 0.5 taken to indicate a large amount of unexplained variance [32, 58, 71]. Factor loadings were considered meaningful if they exceed 0.40 [34], but to assess cross-loading, the loading estimates should be below 0.30 [72].

2.5. Psychometric Properties. The reliability, validity, and responsiveness of the HQ were assessed. All statistical analyses were performed in SPSS (v.22.0).

2.5.1. Reliability: Internal Consistency. Internal consistency was measured as Cronbach's alpha with estimates $\alpha > 0.7$ and $\alpha < 0.9$ taken to indicate acceptable internal consistency [32, 73].

2.5.2. Validity: Convergent and Discriminant Validity. Convergent validity and discriminant validity were evaluated as Spearman's bivariate correlations. Due to the close relationship between tinnitus and hypersensitivity to sound (common problems with concentration/attention, stress, hearing difficulties, participation), the HQ was predicted to moderately correlate with tinnitus questionnaires, that is, moderate discriminant validity. The HQ was predicted to also show moderate correlations with generalised depression and anxiety, because hypersensitivity to sound is associated with both [8, 74].

2.5.3. Responsiveness: Floor and Ceiling Effects. The HQ was not designed for use as an outcome measure; however, some studies still use it for that purpose [33, 40]. Therefore, we looked for floor and/or ceiling effects which would compromise the reliability and responsiveness of the HQ to meaningful changes, although this does not necessarily reflect "real world" change. Response frequency distributions were examined to detect floor or ceiling effects at item level. Floor or ceiling effects were identified as items where more than 15% of respondents rated the lowest or highest possible response option ("no" (0) or "yes, a lot" (3) on a 4-point scale) [32]. Problematic items with floor effects are unlikely to detect reductions in hypersensitivity, whilst items with ceiling effects have limited sensitivity to increases in hypersensitivity.

3. Results

3.1. Inspection of the Distribution of Scores. Descriptive statistics for all questionnaire measures are shown in Table 1. Mean scores for all the questionnaires were at the lower end of the scoring range, with BDI, BAI, and BDI-FS recording the lowest means relative to their maximum possible score. Scores for tinnitus severity in relation to the THI grading system were moderate (<38/100 in each case). Frequency distributions for global HQ scores are given in Figure 2. The HQ scores were slightly skewed towards the lower end of the scales, with a mean score of 14.7. This mean score was almost identical to the mean questionnaire score (15.0) identified by Khalfa and colleagues [31]. Just under half the participants (124 out of 264) were above 14.7, whilst only 19 out of the 264 participants were above 28 and therefore were identified as experiencing hyperacusis.

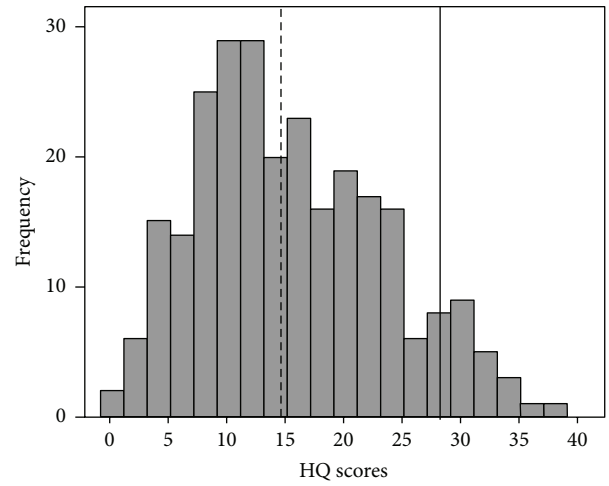


Figure 2: Distribution of Hyperacusis Questionnaire total scores. The diagnostic criterion is represented with a black bold line (—). The mean score for the current study is presented as a black bold dotted line (- - - - -). According to the criteria identified by Khalfa et al. [31], only 7% of participants indicate hypersensitivity, whilst 47% of participants were above our mean score.

3.2. Factor Structure: Confirmatory Factor Analysis

3.2.1. Three Factor Structure. First-order factor correlations, standardised factor loadings, standard error, and squared standardised factor loadings for the observed variables and latent constructs are summarised in Table 2. Correlations between the first-order factors (three subscales) were above 0.70 (Table 2), indicating that there was a degree of overlap between the factors.

Model fit was poor; the WLSMV χ^2 was significant (280.77 (df = 75), $p < 0.001$), and relative to the degrees of freedom, the estimate was significantly higher (3.74) than the critical ratio cutoff (≤2.0). Although the TLI (0.92) and CFI (0.94) were both within the acceptable criteria (marginally below 0.95), both the RMSEA (0.1; CI = 0.09–0.12) and WRMR (1.28) estimates were exceptionally higher than the *a priori* cutoff for establishing adequate fit.

Examination of the squared standardised factor loadings showed that all three first-order factors (attentional, social, and emotional) had high loading values with the second-order factor (over 70% of variance). The loading values for the items ranged from 0.09 to 0.87, with the majority above 0.4. For ten items over 50% of the variance was explained by the first-order factor in which the items are assigned to. For the remaining four items, the standardised factor loadings were low (<0.6), with item 1 below acceptable (0.3). The squared loading values mirrored these loadings (<0.4). The social factor only explained 32% of the variance in items 5 and 6, the emotional factor explained 33% variance in item 11, and the attentional factor only explained an unacceptable 9% variance in item 1. There is a large amount of measurement error that the model cannot explain.

Examination of the modification index revealed the presence of 18 large modification indices (>10). These MIs indicated serious cross-loading between each factor and a number of items. The EPC values indicate that if these parameters were freely estimated, then the improvement to the model would be marginal. Due to the amount of MIs, the small EPC values, and the fact that the model has poor fit statistics, it would make no logical sense to adjust these parameters. A one-factor model might provide a better explanation for the data.

3.2.2. One-Factor Structure. Model fit again was poor; the WLSMV χ^2 (429.88 (df = 77), $p < 0.001$) and all approximation fit indices failed to meet criteria for a good fit. The squared standardised factor loadings indicated the same problematic items (Table 2). The correct χ^2 difference tests

Table 2: Standardised factor loadings (standard error), R-squared values, and factor correlations for the three-factor model and one-factor model of the Hyperacusis Questionnaire.

	Three-factor model				One-factor model	
	$F1$	$F2$	$F3$	R^2	$F1$	R^2
Items						
HQ1	0.30 (0.07)			**0.09**	0.23 (0.10)	0.05
HQ2	0.74 (0.04)			0.54	0.73 (0.05)	0.54
HQ3	0.78 (0.03)			0.60	0.73 (0.05)	0.53
HQ4	0.94 (0.02)			0.87	0.85 (0.03)	0.72
HQ5		0.57 (0.05)		**0.32**	0.55 (0.07)	0.31
HQ6		0.57 (0.06)		**0.32**	0.65 (0.06)	0.42
HQ7		0.75 (0.05)		0.57	0.77 (0.05)	0.59
HQ8		0.73 (0.04)		0.51	0.65 (0.05)	0.43
HQ9		0.83 (0.03)		0.69	0.80 (0.04)	0.64
HQ10		0.84 (0.04)		0.70	0.80 (0.05)	0.64
HQ11			0.50 (0.05)	**0.33**	0.52 (0.07)	0.27
HQ12			0.82 (0.03)	0.73	0.81 (0.04)	0.66
HQ13			0.72 (0.05)	0.60	0.66 (0.06)	0.43
HQ14			0.84 (0.03)	0.66	0.76 (0.04)	0.57
Construct						
Hypersensitivity to sound	0.88 (0.03)	0.86 (0.03)	0.87 (0.03)	—	—	—
R^2	0.77	0.75	0.75	—	—	—
Factor correlations						
$F1$	1			—	—	—
$F2$	0.75 (0.04)	1		—	—	—
$F3$	0.77 (0.03)	0.75 (0.04)	1	—	—	—

The factor loadings (standard errors) and squared factor loadings (R-squared) for the 14 items and the first-order factors (three-factor model only). The values presented in bold have poor associations with their designated factor, all below the recommended cutoff < 0.40. The correlations between the first-order factors were all strong. R^2 = R-squared. α = Cronbach's alpha. HQ = Hyperacusis Questionnaire; $F1$ = attentional; $F2$ = social; $F3$ = emotional.

Table 3: Exploratory factor analysis: factor loadings, communalities, and eigenvalues for the two-factor extraction.

	Items	$F1$	$F2$	Communality
HQ2	Harder to ignore sounds in everyday situations	**0.48**	0.22	0.38
HQ3	Trouble reading in noise	**0.79**	−0.02	0.61
HQ4	Trouble concentrating in noise	**0.83**	0.11	0.79
HQ7	Particularly sensitive to or bothered by noise	0.37	0.37	0.41
HQ8	Noise unpleasant in certain situations	0.18	**0.62**	0.52
HQ9	Think about the noise before going out	−0.04	**0.97**	0.90
HQ10	Turn down invitation because of noise	0.04	**0.85**	0.75
HQ12	Stress and tired ness reduce ability to concentrate	**0.95**	−0.20	0.75
HQ13	Less able to concentrate at end of day	**0.81**	0.02	0.67
HQ14	Certain sounds cause stress and irritation	**0.49**	0.34	0.51
	Eigenvalues	5.25	1.40	—

The factor loading estimates presented in bold are above the recommended cutoff (>0.4) and indicate which factor the item is associated with. Two items show cross-loading, with estimates above 0.3 on the second factor for item 14, whilst item 7 does not load onto either factor. $F1$ = attentional; $F2$ = social.

indicate that the restricted one-factor model significantly degrades the fit of the model ($\chi^2_{\text{diff}}(2) = 108.573$, $p < 0.001$). These findings suggest that one-factor model does not provide an alternative solution for the data.

3.2.3. Exploratory Factor Analysis. Having removed the four problematic items identified in both CFA models (items 1, 5, 6, and 11), the data from sample B was modelled using WLSMV and oblique rotations estimates. Examination of the eigenvalues (>1) and scree plot revealed a two-factor solution (Table 3). Factor 1 consists of 6 items (attentional items) and factor 2 consists of 3 items (social items). One item (Item 7) did not load onto either factor, with low loading estimates across both (<0.4). Items have loading estimates above the desired criteria and show minimal evidence of cross-loading, except for item 14. For the most part, the communalities were

Table 4: Interitem correlations between all fourteen items of the Hyperacusis Questionnaire.

		Attentional				Social						Emotional			
		Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
Attentional	Q1	1													
	Q2	**0.20**	1												
	Q3	**0.12**	0.46	1											
	Q4	**0.17**	0.54	0.69	1										
Social	Q5	**0.16**	0.29	0.31	0.42	1									
	Q6	**0.13**	0.36	**0.25**	0.32	**0.20**	1								
	Q7	**0.15**	0.46	0.37	0.50	**0.21**	0.31	1							
	Q8	**0.16**	0.34	0.32	0.41	0.42	**0.29**	0.36	1						
	Q9	**0.17**	0.38	0.35	0.38	**0.22**	**0.29**	0.35	0.53	1					
	Q10	**0.15**	0.30	**0.24**	0.34	**0.17**	**0.27**	0.32	0.45	0.72	1				
Emotional	Q11	**0.06**	0.32	0.34	0.33	**0.17**	0.30	**0.28**	**0.21**	0.31	**0.23**	1			
	Q12	**0.20**	0.43	0.47	0.55	0.36	**0.29**	0.38	0.35	0.30	0.29	0.38	1		
	Q13	**0.18**	0.34	0.38	0.48	**0.29**	**0.17**	0.31	**0.26**	0.31	0.33	0.36	0.69	1	
	Q14	**0.14**	0.42	0.42	0.53	0.35	0.33	0.54	0.45	0.44	0.38	0.39	0.48	0.42	1

Correlations ranged from extremely low to high. The majority of the items showing low to moderate correlations with each other.
Correlations presented in bold are below the recommended cutoff (0.3), indicating weak relationships between items.

acceptable (>0.50), expect for item 2 and again item 7 which were below < 0.4. Low loading and the low communality suggest that item 7 is unrelated to the underlying construct being measured by the two factors and therefore provides little information on hypersensitivity. Finally the two factors moderately correlated with each other indicating that they are measuring different aspects of hypersensitivity.

3.3. Reliability: Internal Consistency. Interitem correlations are presented in Table 4. The correlations ranged from 0.06 to 0.72. Item 1 displayed extremely low correlations with the rest of the items (<0.2), particularly with item 11 (0.06) indicating no relationship between the item contents. The interitem correlations for the social subscale indicate that items 5 and 6 are unrelated (<0.3) to the other items in the subscale indicating poor internal consistency. The rest of the items have low to moderate correlation with each other, suggesting variability in item content. Only one correlation, between item 9 and item 10, indicates high internal consistency (above 0.7). In contrast, Cronbach's alpha estimates for the HQ global score were high (α = 0.88) and subscale scores were all above the specified criteria ($\alpha > 0.7$).

3.4. Validity. Convergent validity between the HQ and ULLs was moderate ($r = -0.535$) suggesting that the two tools are measuring different constructs with some association. Discriminant validity was as predicted (Table 5). HQ scores showed moderate positive correlations with the two measures of tinnitus severity (THI and THQ) and the three general health measures (BDI, BDI-FS, and BAI). Therefore, with regard to these measures, the HQ demonstrates acceptable discriminant validity indicating that it measures construct(s) that are distinct from tinnitus specific and more general health domains.

Table 5: Correlations between the global scores of the six questionnaire measures.

	HQ	THI	THQ	BDI-II	BDI-FS	BAI
HQ	1					
THI	0.49	1				
THQ	0.40	0.66	1			
BDI-II	0.37	0.45	0.47	1		
BDI-FS	0.32	—	0.21	—	1	
BAI	0.38	0.38	0.28	0.68	0.48	1

The correlations between the HQ and all other measures were moderate indicating acceptable discriminant validity. HQ = Hyperacusis Questionnaire; THI = Tinnitus Handicap Inventory; THQ = Tinnitus Handicap Questionnaire, BDI-II = Beck's Depression Inventory-II, BDI-FS = Beck's Depression Inventory-Fast Screen; BAI = Beck's Anxiety Inventory.

3.5. Responsiveness: Floor and Ceiling Effects. Response frequency distributions for each HQ item are displayed in Table 6. All fourteen items failed to meet the a priori criterion for acceptable floor and ceiling effects. Twelve items (items 4, 12, 14, 13, 3, 2, 11, 9, 7, 1, 10, and 6) showed floor effects, with 17% to 71% of participants scoring "0." Item 6 (70%), item 10 (68%), and item 1 (68%) had extreme floor effect with over two-thirds of participants scoring "0." Two out of the twelve items (items 4 and 12) that showed floor effects also showed mild ceiling effects, with 17% of participants scoring "3." The remaining two items (items 8 and 5) showed ceiling effects, with 25% and 45% of participants, scoring "3," respectively. Therefore, these response options are not reliably distinguishing between participants and cannot be considered responsive to changes, at least in this particular population.

4. Discussion

The current study evaluated psychometric properties of the HQ in a large UK population of research participants with

Table 6: Response frequency distributions (%) for each Hyperacusis Questionnaire item.

		Frequency of responses for items (%)				Mean	(±SD)
		0	1	2	3		
1	Use earplugs or earmuffs to reduce noise	**67.8**	24.2	4.5	3.4	0.44	(0.74)
2	Harder to ignore sounds in everyday situations	**34.5**	37.9	19.7	8.0	1.01	(0.93)
3	Trouble reading in noise	**31.8**	33.3	22.7	12.1	1.15	(1.01)
4	Trouble concentrating in noise	**17.4**	35.2	30.3	**17.0**	1.47	(0.97)
5	Difficulty listening to conversations in noise	8.7	20.1	28.4	**42.8**	2.05	(0.99)
6	Tolerate noise badly	**70.5**	17.8	5.7	6.1	0.47	(0.85)
7	Particularly sensitive to or bothered by noise	**54.5**	32.2	10.6	2.7	0.61	(0.78)
8	Noise unpleasant in certain situations	13.6	31.8	29.5	**25.0**	1.66	(1.00)
9	Think about the noise before going out	**52.7**	24.2	12.9	10.2	0.81	(1.02)
10	Turn down invitation because of noise	**68.2**	19.7	7.2	4.9	0.49	(0.83)
11	Sounds bother you more in quiet places than noisy	**39.0**	36.4	15.9	8.7	0.94	(0.95)
12	Stress and tired ness reduce ability to concentrate	**19.3**	39.0	25.0	**16.7**	1.39	(0.98)
13	Less able to concentrate at end of day	**29.9**	37.1	22.0	11.0	1.14	(0.97)
14	Certain sounds cause stress and irritation	**22.3**	41.3	23.9	12.5	1.27	(0.95)

Response frequency distributions presented in bold indicate that more than 15% of respondents rated the lowest or highest possible response option. All fourteen items showed either floor or/and ceiling effects (>15%).

tinnitus. Despite the high internal consistency estimates, analyses did not confirm the original three factor solution proposed by Khalfa et al. [31] for our UK research population data. Large amounts of cross-loading between the questionnaire items and high correlations between the factors suggested that a one-factor solution is more likely optimal. However, a one-factor solution similarly indicated a poor fit. Four out of 14 items (items 1, 5, 6, and 11) had factor loadings below 0.4 in both models tested potentially suggesting that the wording of these problematic items in relation to this particular population is more likely the cause of poor fit in the three-factor solution. The poor fit could at least in part be due to some population (tinnitus specific) factors. Item 1 asks *"Do you ever use earplugs or earmuffs to reduce your noise perception?"* and although intended to assess attentional component of hyperacusis in a general population [31], within a tinnitus population using ear protection in normal environments is not encouraged, hence the possibility that people with tinnitus will refrain from using earplugs or ear muffs. Item 6 also showed floor effects; it asks *"Has anyone you know ever told you that you tolerate noise or certain kinds of sound badly?"*. The floor effects seen in this item could potentially reflect the management strategy for tinnitus such as sound therapy and exposure to moderate levels of background noise; in particular, tinnitus habituation therapies (e.g., tinnitus retraining therapy) combine education with sound [75, 76]. Item 5 asks "*Do you have difficulty listening to conversations in noisy places?*". A possible reason it might not fit with the social subscale is that similar difficulties are reported due to hearing loss and tinnitus but not necessarily to hypersensitivity to sound. Finally, item 11 asks *"Do noises or particular sounds bother you more in a quiet place than in a slightly noisy room?"*. Some people with tinnitus will use background noise to "drown out" or mask their tinnitus, while quiet environment can exacerbate their tinnitus and so generally tend to avoid quiet [77]. Consequently, these items were removed and a two-factor solution, with an attentional and social component with the 10 items was identified using exploratory factor analysis.

In terms of convergent and discriminant validity, moderate correlations were observed for all measures suggesting that the HQ is measuring an alternative construct to these measures; in particular, the HQ measures a construct that is different to the sensitivity to loud sounds measured as ULLs. However, due to the differences in measures used to test convergent and discriminant validity (a psychoacoustic test and questionnaires, resp.), it is hard to definitively establish the level of discriminant validity. To provide clarity on this, one recommendation for future studies is to assess convergent validity using a questionnaire measure of hyperacusis.

It is worth noting that only 19 out of 264 participants were classified as hyperacusic according to the criterion of 28 points or more proposed by Khalfa et al. [31]. That indicates the prevalence of hyperacusis in the UK tinnitus research population of about 7.2% which is considerably lower than previously reported for the tinnitus population [10, 12, 13], suggesting that the criterion score might be too high. The criterion score greater than 28 for diagnosing significant hypersensitivity to sound was also questioned by Meeus et al. [33], who reported that most of patients who reported lower tolerance for noise and fear of noise scored below 28 on the HQ.

The HQ was developed to quantify and characterise hypersensitivity to sound and not to be an outcome measure [31]. It is, however, used as an outcome measure [33, 40]. All items showed floor (12 items) or ceiling effects (2 items) with two items showing extreme floor effects where over 60% of participants scored "0." This indicates that those response options do not reliably distinguish between participants and would not be responsive to changes in severity in this

particular population. Therefore, we conclude the 14-item HQ is not a sensitive measure of outcome.

5. Conclusions/Recommendations

(i) The HQ does not provide a valid overall measure of hypersensitivity to sound in the UK population with tinnitus. The structure of the questionnaire was not confirmed. Until an appropriate questionnaire is developed, we recommend the removal of confounding items and evaluation of a 10-item (2-factor) version of the questionnaire in a new tinnitus and perhaps nontinnitus population.

(ii) The diagnostic criterion (28 points) needs to be reevaluated. In order to stratify severity, one suggested method is through the use of anchor questions which can provide external indicators of severity. This strategy has been used in development of the Tinnitus Functional Index and also for identifying meaningful change scores [78–80]. For sensitivity to sound at screening, stratification can be based on response levels in the anchor question, by directly comparing them to the overall score on the questionnaire, providing a practical interpretation of the scores that reflects the patients' opinions.

(iii) A questionnaire measure of sensitivity to sound that is more suitable for use in tinnitus research population should be identified or developed.

(iv) For completeness the HQ needs to be validated in general (including UK) populations, and validation should include test-retest and convergent validity.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Kathryn Fackrell and Constance Fearnley contributed equally to this paper.

Acknowledgments

This report is independent research by the National Institute for Health Research Biomedical Research Unit Funding Scheme. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research, or the Department of Health.

References

[1] J. A. Vernon, "Pathophysiology of tinnitus: a special case—hyperacusis and a proposed treatment," *American Journal of Otology*, vol. 8, no. 3, pp. 201–202, 1987.

[2] A. J. Klein, B. L. Armstrong, M. K. Greer, and F. R. Brown III, "Hyperacusis and otitis media in individuals with williams syndrome," *Journal of Speech and Hearing Disorders*, vol. 55, no. 2, pp. 339–344, 1990.

[3] U. Katzenell and S. Segal, "Hyperacusis: review and clinical guidelines," *Otology & Neurotology*, vol. 22, no. 3, pp. 321–327, 2001.

[4] P. J. Jastreboff and M. M. Jastreboff, "Tinnitus retraining therapy for patients with tinnitus and decreased sound tolerance," *Otolaryngologic Clinics of North America*, vol. 36, no. 2, pp. 321–336, 2003.

[5] D. M. Baguley, "Hyperacusis," *Journal of the Royal Society of Medicine*, vol. 96, no. 12, pp. 582–585, 2003.

[6] A. Fabijanska, M. Rogowski, G. Bartnik et al., "Epidemiology of tinnitus and hyperacusis in Poland," in *Proceeding of the Sixth International Tinnitus Seminar*, J. W. P. Hazell, Ed., pp. 569–571, THC, Cambridge, UK, 1999.

[7] G. Andersson, N. Lindvall, T. Hursti, and P. Carlbring, "Hypersensitivity to sound (hyperacusis): a prevalence study conducted via the internet and post," *International Journal of Audiology*, vol. 41, no. 8, pp. 545–554, 2002.

[8] L. Jüris, G. Andersson, H. C. Larsen, and L. Ekselius, "Cognitive behaviour therapy for hyperacusis: a randomized controlled trial," *Behaviour Research and Therapy*, vol. 54, no. 1, pp. 30–37, 2014.

[9] R. S. Tyler, M. Pienkowski, E. R. Roncancio et al., "A review of hyperacusis and future directions. Part I. Definitions and manifestations," *The American Journal of Audiology*, vol. 23, no. 4, pp. 402–419, 2014.

[10] L. Jüris, G. Andersson, H. C. Larsen, and L. Ekselius, "Psychiatric comorbidity and personality traits in patients with hyperacusis," *International Journal of Audiology*, vol. 52, no. 4, pp. 230–235, 2013.

[11] P. J. Jastreboff and J. Hazell, *Tinnitus Retraining Therapy: Implementing the Neurophysiological Mode*, Cambridge University Press, Cambridge, UK, 2004.

[12] P. J. Jastreboff and M. M. Jastreboff, "Tinnitus retraining therapy (TRT) as a method for treatment of tinnitus and hyperacusis patients," *Journal of the American Academy of Audiology*, vol. 11, no. 3, pp. 162–177, 2000.

[13] M. Anari, A. Axelsson, A. Eliasson, and L. Magnusson, "Hypersensitivity to sound—questionnaire data, audiometry and classification," *Scandinavian Audiology*, vol. 28, no. 4, pp. 219–230, 1999.

[14] J. Marriage and N. M. Barnes, "Is central hyperacusis a symptom of 5-hydroxytryptamine (5-HT) dysfunction?" *The Journal of Laryngology & Otology*, vol. 109, no. 10, pp. 915–921, 1995.

[15] G. C. Thompson, A. M. Thompson, K. M. Garrett, and B. H. Britton, "Serotonin and serotonin receptors in the central auditory system," *Otolaryngology—Head and Neck Surgery*, vol. 110, no. 1, pp. 93–102, 1994.

[16] P. J. Jastreboff and J. W. P. Hazell, "A neurophysiological approach to tinnitus: clinical implications," *British Journal of Audiology*, vol. 27, no. 1, pp. 7–17, 1993.

[17] R. Schaette and R. Kempter, "Development of tinnitus-related neuronal hyperactivity through homeostatic plasticity after hearing loss: a computational model," *European Journal of Neuroscience*, vol. 23, no. 11, pp. 3124–3138, 2006.

[18] A. J. Noreña, "An integrative model of tinnitus based on a central gain controlling neural sensitivity," *Neuroscience and Biobehavioral Reviews*, vol. 35, no. 5, pp. 1089–1109, 2011.

[19] J. W. Gu, C. F. Halpin, E.-C. Nam, R. A. Levine, and J. R. Melcher, "Tinnitus, diminished sound-level tolerance, and elevated auditory activity in humans with clinically normal hearing sensitivity," *Journal of Neurophysiology*, vol. 104, no. 6, pp. 3361–3370, 2010.

[20] W. Hiller and G. Goebel, "Factors influencing tinnitus loudness and annoyance," *Archives of Otolaryngology—Head and Neck Surgery*, vol. 132, no. 12, pp. 1323–1330, 2006.

[21] M. Fusetti, A. B. Fioretti, and A. Eibenstein, "Association between sleep disorders, hyperacusis and tinnitus: evaluation with tinnitus questionnaires," *Noise and Health*, vol. 15, no. 63, pp. 91–95, 2013.

[22] P. J. Jastreboff and M. M. Jastreboff, "Treatments for decreased sound tolerance (hyperacusis and misophonia)," *Seminars in Hearing*, vol. 35, no. 2, pp. 105–120, 2014.

[23] A. Axelsson and M. Anari, "Hyperacusis," *Zeitschrift für Lärmbekämpfung*, vol. 42, no. 1, pp. 18–20, 1995.

[24] J. K. Dawson Jr., "A comparison of physical measurements of pure-tones, third-octave bands of noise and third-octave bands of speech to subjective judgments of audibility threshold, MCL and UCL for three normally hearing listeners," Independent Studies and Capstones Paper No. 306, Washington University School of Medicine, Program in Audiology and Communication Sciences, St. Louis, Mo, USA, 1981.

[25] D. M. Hawkins, *Monographs on Applied Probability and Statistics*, Chapman & Hall, London, UK, 1980.

[26] D. Baguley and G. Andersson, *Hyperacusis: Mechanisms, Diagnosis, and Therapies*, Plural Publishing, San Diego, Calif, USA, 2007.

[27] M. Nelting and N. K. Finlayson, *G Ü F-Geräuschüberempfindlichkeits-Fragebogen*, Hogrefe, Göttingen, Germany, 2004.

[28] L. Bläsing, G. Goebel, U. Flötzinger, A. Berthold, and B. Kröner-Herwig, "Hypersensitivity to sound in tinnitus patients: an analysis of a construct based on questionnaire and audiological data," *International Journal of Audiology*, vol. 49, no. 7, pp. 518–526, 2010.

[29] L. Blaesing and B. Kroener-Herwig, "Self-reported and behavioral sound avoidance in tinnitus and hyperacusis subjects, and association with anxiety ratings," *International Journal of Audiology*, vol. 51, no. 8, pp. 611–617, 2012.

[30] R. Dauman and F. Bouscau-Faure, "Assessment and amelioration of hyperacusis in tinnitus patients," *Acta Oto-Laryngologica*, vol. 125, no. 5, pp. 503–509, 2005.

[31] S. Khalfa, S. Dubal, E. Veuillet, F. Perez-Diaz, R. Jouvent, and L. Collet, "Psychometric normalization of a hyperacusis questionnaire," *ORL Journal for Oto-Rhino-Laryngology and its Related Specialities*, vol. 64, no. 6, pp. 436–442, 2002.

[32] C. B. Terwee, S. D. M. Bot, M. R. de Boer et al., "Quality criteria were proposed for measurement properties of health status questionnaires," *Journal of Clinical Epidemiology*, vol. 60, no. 1, pp. 34–42, 2007.

[33] O. M. Meeus, M. Spaepen, D. De Ridder, and P. H. Van de Heyning, "Correlation between hyperacusis measurements in daily ENT practice," *International Journal of Audiology*, vol. 49, no. 1, pp. 7–13, 2010.

[34] F. J. Floyd and K. F. Widaman, "Factor analysis in the development and refinement of clinical assessment instruments," *Psychological Assessment*, vol. 7, no. 3, pp. 286–299, 1995.

[35] H. C. W. de Vet, H. J. Adèr, C. B. Terwee, and F. Pouwer, "Are factor analytical techniques used appropriately in the validation of health status questionnaires? A systematic review on the quality of factor analysis of the SF-36," *Quality of Life Research*, vol. 14, no. 5, pp. 1203–1218, 2005.

[36] S. Blomberg, M. Rosander, and G. Andersson, "Fears, hyperacusis and musicality in Williams syndrome," *Research in Developmental Disabilities*, vol. 27, no. 6, pp. 668–680, 2006.

[37] S. Hébert and J. Carrier, "Sleep complaints in elderly tinnitus patients: a controlled study," *Ear and Hearing*, vol. 28, no. 5, pp. 649–655, 2007.

[38] P. Adjamian, M. Sereda, O. Zobay, D. A. Hall, and A. R. Palmer, "Neuromagnetic indicators of tinnitus and tinnitus masking in patients with and without hearing loss," *Journal of the Association for Research in Otolaryngology*, vol. 13, no. 5, pp. 715–731, 2012.

[39] M. Sereda, P. Adjamian, M. Edmondson-Jones, A. R. Palmer, and D. A. Hall, "Auditory evoked magnetic fields in individuals with tinnitus," *Hearing Research*, vol. 302, pp. 50–59, 2013.

[40] D. J. Hoare, V. L. Kowalkowski, and D. A. Hall, "Effects of frequency discrimination training on tinnitus: results from two randomised controlled trials," *Journal of the Association for Research in Otolaryngology*, vol. 13, no. 4, pp. 543–559, 2012.

[41] D. J. Hoare, N. Van Labeke, A. McCormack et al., "Gameplay as a source of intrinsic motivation in a randomized controlled trial of auditory training for tinnitus," *PLoS ONE*, vol. 9, no. 9, Article ID e107430, 2014.

[42] D. J. Hoare, M. Edmondson-Jones, P. E. Gander, and D. A. Hall, "Agreement and reliability of tinnitus loudness matching and pitch likeness rating," *PLoS ONE*, vol. 9, no. 12, Article ID e114553, 2014.

[43] J. Davies, P. E. Gander, M. Andrews, and D. A. Hall, "Auditory network connectivity in tinnitus patients: a resting-state fMRI study," *International Journal of Audiology*, vol. 53, no. 3, pp. 192–198, 2014.

[44] M. Sereda, J. Davies, and D. A. Hall, "Evaluating a pre-market version of Oticon Alta with a Tinnitus Sound Generator: Tinnitus relief," in *Proceedings of the British Academy of Audiology 11th Annual Conference*, Bournemouth, UK, November 2014.

[45] F. K. Kuk, R. S. Tyler, D. Russell, and H. Jordan, "The psychometric properties of a tinnitus handicap questionnaire," *Ear & Hearing*, vol. 11, no. 6, pp. 434–445, 1990.

[46] C. W. Newman, G. P. Jacobson, and J. B. Spitzer, "Development of the tinnitus handicap inventory," *Otolaryngology—Head & Neck Surgery*, vol. 122, no. 2, pp. 143–148, 1996.

[47] A. T. Beck, R. A. Steer, and G. K. Brown, *BDI-II, Beck Depression Inventory: Manual*, Harcourt Brace, Boston, Mass, USA, 2nd edition, 1996.

[48] A. T. Beck, N. Epstein, G. Brown, and R. A. Steer, "An inventory for measuring clinical anxiety: Psychometric properties," *Journal of Consulting and Clinical Psychology*, vol. 56, no. 6, pp. 893–897, 1988.

[49] A. T. Beck, R. A. Steer, and G. K. Brown, *BDI-FS Screen for Medical Inpatients: Manual*, Psychological Corporation, San Antonio, Tex, USA, 2000.

[50] D. M. Baguley, R. L. Humphriss, and C. A. Hodgson, "Convergent validity of the tinnitus handicap inventory and the tinnitus questionnaire," *The Journal of Laryngology and Otology*, vol. 114, no. 11, pp. 840–843, 2000.

[51] A. McCombe, D. Baguley, R. Coles, L. McKenna, C. McKinney, and P. Windle-Taylor, "Guidelines for the grading of tinnitus severity: the results of a working group commissioned by the British Association of Otolaryngologists, Head and Neck Surgeons, 1999," *Clinical Otolaryngology and Allied Sciences*, vol. 26, no. 5, pp. 388–393, 2001.

[52] D. M. Baguley and G. Andersson, "Factor analysis of the tinnitus handicap inventory," *American Journal of Audiology*, vol. 12, no. 1, pp. 31–34, 2003.

[53] P. J. Brantley, G. R. Dutton, and K. B. Wood, "The Beck Depression Inventory-II (BDI-II) and the beck depression inventory—primary care," in *The Use of Psychological Testing for Treatment Planning and Assessment Outcome*, vol. 3, pp. 313–326, 2004.

[54] D. L. Segal, F. L. Coolidge, B. S. Cahill, and A. A. O'Riley, "Psychometric properties of the beck depression inventory—II (BDI-II) among community-dwelling older adults," *Behavior Modification*, vol. 32, no. 1, pp. 3–20, 2008.

[55] A. T. Beck and R. A. Steer, *Manual for the Beck Anxiety Inventory*, Psychological Corporation, San Antonio, Tex, USA, 1990.

[56] O. T. Leyfer, J. L. Ruberg, and J. Woodruff-Borden, "Examination of the utility of the Beck Anxiety Inventory and its factors as a screener for anxiety disorders," *Journal of Anxiety Disorders*, vol. 20, no. 4, pp. 444–458, 2006.

[57] L. K. Muthén and B. O. Muthén, *Mplus User's Guide*, Muthén & Muthén, Los Angeles, Calif, USA, 7th edition, 1998–2012.

[58] T. A. Brown, *Confirmatory Factor Analysis for Applied Research*, The Guilford Press, New York, NY, USA, 2006.

[59] D. B. Flora and P. J. Curran, "An empirical evaluation of alternative methods of estimation for confirmatory factor analysis with ordinal data," *Psychological Methods*, vol. 9, no. 4, pp. 466–491, 2004.

[60] T. A. Brown and M. T. Moore, "Confirmatory factor analysis," in *Handbook of Structural Equation Modelling*, R. H. Hoyle, Ed., pp. 361–379, Guilford Press, 2012.

[61] B. O. Muthén, S. H. C. du Toit, and D. Spisic, "Robust inference using Weighted Least Squares and Quadratic Estimating Equations in Latent Variable Modeling with Categorical and Continuous Outcomes," 1997, https://www.statmodel.com/wlscv.shtml.

[62] P. M. Bentler, "Comparative fit indexes in structural models," *Psychological Bulletin*, vol. 107, no. 2, pp. 238–246, 1990.

[63] L. R. Tucker and C. Lewis, "A reliability coefficient for maximum likelihood factor analysis," *Psychometrika*, vol. 38, no. 1, pp. 1–10, 1973.

[64] L.-T. Hu and P. M. Bentler, "Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives," *Structural Equation Modeling*, vol. 6, no. 1, pp. 1–55, 1999.

[65] J. H. Steiger and J. C. Lind, "Statistically based tests for the number of common factors," in *Proceedings of the Annual Meeting of the Psychometric Society*, Iowa City, Iowa, USA, 1980.

[66] C. Y. Yu, *Evaluating cutoff criteria of model fit indices for latent variable models with binary and continuous outcomes [Ph.D. dissertation]*, University of California, Los Angeles, Los Angeles, Calif, USA, 2002.

[67] L.-T. Hu and P. M. Bentler, "Fit indices in covariance structure modeling: sensitivity to underparameterized model misspecification," *Psychological Methods*, vol. 3, no. 4, pp. 424–453, 1998.

[68] R. C. MacCallum, M. Roznowski, and L. B. Necowitz, "Model modifications in covariance structure analysis: the problem of capitalization on chance," *Psychological Bulletin*, vol. 111, no. 3, pp. 490–504, 1992.

[69] S. P. Reise, N. G. Waller, and A. L. Comrey, "Factor analysis and scale revision," *Psychological Assessment*, vol. 12, no. 3, pp. 287–297, 2000.

[70] H. F. Kaiser, "The application of electronic computers to factor analysis," *Educational and Psychological Measurement*, vol. 20, no. 1, pp. 141–151, 1960.

[71] L. R. Fabrigar, D. T. Wegener, R. C. MacCallum, and E. J. Strahan, "Evaluating the use of exploratory factor analysis in psychological research," *Psychological Methods*, vol. 4, no. 3, pp. 272–299, 1999.

[72] B. G. Tabachnick and L. S. Fidell, *Using Multivariate Statistics*, Pearson, Boston, Mass, USA, 6th edition, 2013.

[73] R. A. Peterson, "A Meta-Analysis of Cronbach's Coefficient Alpha," *Journal of Consumer Research*, vol. 21, no. 2, p. 381, 1994.

[74] T. L. Sahley and R. H. Nodar, "A biochemical model of peripheral tinnitus," *Hearing Research*, vol. 152, no. 1-2, pp. 43–54, 2001.

[75] P. J. Jastreboff, "Tinnitus retraining therapy," *Progress in Brain Research*, vol. 166, pp. 415–423, 2007.

[76] J. S. Philips, D. McFerran, and J. S. Philips, "Tinnitus Retraining Therapy (TRT) for tinnitus," *Cochrane Database of Systematic Reviews*, vol. 3, Article ID CD007330, 2010.

[77] J. Hobson, E. Chisholm, and A. El Refaie, "Sound therapy (masking) in the management of tinnitus in adults," *Cochrane Database of Systematic Reviews*, vol. 11, Article ID CD006371, 2012.

[78] H. C. de Vet, C. B. Terwee, R. W. Ostelo, H. Beckerman, D. L. Knol, and L. M. Bouter, "Minimal changes in health status questionnaires: distinction between minimally detectable change and minimally important change," *Health and Quality of Life Outcomes*, vol. 4, article 54, 2006.

[79] D. Revicki, R. D. Hays, D. Cella, and J. Sloan, "Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes," *Journal of Clinical Epidemiology*, vol. 61, no. 2, pp. 102–109, 2008.

[80] M. B. Meikle, J. A. Henry, S. E. Griest et al., "The tinnitus functional index: development of a new clinical measure for chronic, intrusive tinnitus," *Ear and Hearing*, vol. 33, no. 2, pp. 153–176, 2012.

Hindawi Publishing Corporation
BioMed Research International
Volume 2015, Article ID 191479, 7 pages
http://dx.doi.org/10.1155/2015/191479

Research Article

Validation of Screening Questions for Hyperacusis in Chronic Tinnitus

Martin Schecklmann,[1,2] Astrid Lehner,[1,2] Winfried Schlee,[1,2] Veronika Vielsmeier,[2,3] Michael Landgrebe,[4] and Berthold Langguth[1,2]

[1] *Department of Psychiatry and Psychotherapy, University of Regensburg, Germany*
[2] *Interdisciplinary Tinnitus Center, University of Regensburg, Regensburg, Germany*
[3] *Department of Otolaryngology, University of Regensburg, Germany*
[4] *Department of Psychiatry and Psychotherapy, Kbo-Lech-Mangfall-Klinik, Hausham, Germany*

Correspondence should be addressed to Martin Schecklmann; martin.schecklmann@medbo.de

Received 13 April 2015; Accepted 15 June 2015

Academic Editor: Aage R. Møller

Background. We investigated the validity of the two hyperacusis items of the TSCHQ (Tinnitus Sample Case History Questionnaire) from the TRI (Tinnitus Research Initiative) database by comparing them with the German hyperacusis questionnaire GÜF. *Methods.* We investigated the association of the GÜF with the TSCHQ screening questions for both the sum score and the single items with correlation, contrast, principal component, and discriminant analysis in a sample of 161 patients with chronic tinnitus. *Results.* TSCHQ items and the GÜF total score were significantly associated with a special focus on fear and pain related hyperacusis. Factor analysis of the GÜF revealed the three factors "fear and pain related hyperacusis," "hearing related problems," and "problems in quality of life." A discriminant analysis showed a sensitivity of 64% and a specificity of 71% of the TSCHQ items for the establishment of tinnitus patient subgroups with and without hyperacusis. *Discussion.* Both hyperacusis TSCHQ items can serve as screening questions with respect to self-reported hyperacusis in chronic tinnitus with a specific focus on fear and pain related hyperacusis. However, the multiple dimensions of hyperacusis should be considered for diagnosis and treatment in both scientific and clinical contexts.

1. Introduction

Hyperacusis has several definitions, but all of them include intolerance to "normal" sounds [1]. "Normal" is defined as an intensity or volume of a perceived sound that would not bother a person with "standard" hearing. Hyperacusis is described in terms of discomfort, pain, hypersensitivity, or hyperresponsiveness and can be related to the domains "loudness," "annoyance," "fear," and "pain" [2]. The importance of anxiety and avoidance behavior in hyperacusis was recently corroborated [3].

Two inventories exist for the assessment of hyperacusis. The first inventory differentiates hyperacusis into the factors "cognitive reactions to hyperacusis," "actional/somatic behavior," and "emotional reaction to external noises" (Geräuschüberempfindlichkeitsfragebogen; GÜF: engl. hypersensitivity to sound questionnaire) [4]; the second defines it using attentional, social, and emotional dimensions (hyperacusis questionnaire; HQ) [5].

From a psychoacoustical perspective, hyperacusis is related to loudness recruitment. Loudness recruitment can usually be found in hearing loss with abnormal rapid increases of perceived loudness with increasing sound intensity [6]. There is evidence that hyperacusis and loudness recruitment are not identical [7], but the two phenomena are also not exclusive from each other [2, 6].

The analysis of a large tinnitus database [8] revealed that hyperacusis is highly prevalent among patients with chronic tinnitus and that hyperacusis characterizes a specific subtype of tinnitus patients with a greater need for treatment [9]. Thus, screening tools for hyperacusis are necessary in the diagnostic assessment of chronic tinnitus. We investigated the validity of the two hyperacusis items ("Do you have a problem

tolerating sounds because they often seem much too loud? i.e., do you often find too loud or hurtful sounds which other people around you find quite comfortable?" "Do sounds cause you pain or physical discomfort?") of the TSCHQ (Tinnitus Sample Case History Questionnaire) [10] from the TRI (Tinnitus Research Initiative) database [8], by correlating them with the German GÜF. First, we specified descriptive data of the different hyperacusis measures in a sample of 161 patients with chronic tinnitus. Second, we investigated the association of the screening items with the GÜF sum score using correlational analyses. Further fine-grained analyses included linear discriminant, principal component, and correlation analyses with tinnitus-specific and tinnitus-unspecific parameters to assess the dimensions of hyperacusis which can be measured with the screening items. These analyses were performed to assess the validity of the TSCHQ screening items as screening parameters for hyperacusis as identified with the GÜF.

2. Materials and Methods

The 161 subjects were patients of the Interdisciplinary Tinnitus Center at the University of Regensburg (Regensburg, Germany). Tinnitus diagnosis at the Department of Otorhinolaryngology and the Department of Psychiatry included a complete otologic and audiologic examination with pure tone audiometry, tympanometry, and otoscopy. Patients gave written informed consent for their data to be used in the Tinnitus Research Initiative database which was approved by the Ethics Committee of the University Hospital of Regensburg (Germany; reference number 08/046).

Patients completed the tinnitus questionnaire (TQ; range: 0–84) [11, 12], the Tinnitus Handicap Inventory (range: 0–100) [13], five numeric rating scales for the assessment of tinnitus loudness, annoyance, discomfort, ignorability, and unpleasantness (scale: 0–10), the Geräuschüberempfindlichkeitsfragebogen (GÜF; engl. hypersensitivity to sound questionnaire; range 0–45) [4], a German version of a quality of life scale (WHOQOL-BREF; scores 4–20) [14], and the Beck depression inventory (BDI; range: 0–63) [15]. In the quality of life scale high scores indicate high quality of life; in all other scales high scores indicate high burden. The TQ contains different subscales: emotional distress, cognitive distress, sleep disturbance, auditory perceptual difficulties, somatic complaints, and intrusiveness.

We used the two screening questions for hyperacusis as indicated by the Tinnitus Sample Case History Questionnaire [10]: (1) "Do you have a problem tolerating sounds because they often seem much too loud? That is, do you often find too loud or hurtful sounds which other people around you find quite comfortable?" with the answers "never, rarely, sometimes, usually, or always" on a scale from 1 to 5; (2) "Do sounds cause you pain or physical discomfort?" with the answers "yes, no, or I do not know." We named these screening questions "loudness hyperacusis" and "pain hyperacusis" based on a recent review paper from worldwide hyperacusis experts [2]. They defined loudness hyperacusis as "…present when moderately intense sounds are judged to be very loud compared with what a person with normal hearing would perceive." With respect to pain hyperacusis they state the following: "Some with hyperacusis experience pain at much lower sound levels than listeners with normal hearing."

Statistical analyses were performed with SPSS 22 (SPSS Inc., USA). First, sample characteristics were calculated by using mean ± standard deviation and absolute and relative frequencies of hyperacusis for the sample. Second, we investigated the association of the hyperacusis parameters by correlating the GÜF sum score and the hyperacusis screening questions. Third, based on these analyses we aimed at defining two groups of tinnitus patients, with and without hyperacusis, and calculated a linear discriminant analysis using the GÜF sum score as the independent variable. Fourth, we calculated associations of the screening questions with the single items of the GÜF to investigate the association on a single item level. Complementary, we did a principal component analysis (PCA) with the principal axis factoring method using varimax rotation and three factors to validate the factor structure of the validation of GÜF. The PCA was done with and without the hyperacusis screening items, for the whole sample and for the subgroup with only hyperacusis to test for possible influences of sample and analysis bias. Fifth, we correlated the resulting factors with tinnitus- and non-tinnitus-related parameters to control for the external validity of these factors. Correlation analyses for metric variables were done with Pearson correlation coefficients, for categorical variables with chi-square test of independence, and for mixed metric and categorical variables by using Student's t-tests or analyses of variance (ANOVAs). For PCA, we report the highest factor loading per item.

3. Results

3.1. Sample Characteristics. Patients were 53.4 ± 12.1 years old, 65.8% male (106 of 161), and had a tinnitus duration of 117.4 ± 105.3 (n = 151) months and a tinnitus distress level of 43.7 ± 15.8 as indicated by the TQ and of 51.7 ± 23.6 as indicated by the THI. The BDI showed mild depressivity (8.3 ± 6.0) which was mirrored by diminished quality of life scores (physical health: 14.5 ± 3.2 (n = 159); psychological health: 13.9 ± 2.9 (n = 159); social relationships: 14.5 ± 3.6 (n = 160); environment: 16.4 ± 2.3 (n = 160)). Sixteen (9.9%) showed purely right, 34 (21.1%) purely left, and 111 (69%) tinnitus in both ears or within the head. Mean hearing level was 23.1 ± 15.5 dB HL (n = 148). Numeric ratings were in the upper half of the scale (loudness: 6.7 ± 2.2; discomfort: 7.3 ± 2.2 (n = 159); annoyance: 6.9 ± 2.4; ignorability: 7.0 ± 2.4; unpleasantness: 7.0 ± 2.3). The mean hyperacusis score as obtained by the GÜF was 15.4 ± 9.2. In comparison to the tinnitus sample of the validation paper [4] GÜF values were comparable (17.8 ± 9.2). For the pain hyperacusis screening question, 102 (63.4%) answered with yes and 59 (36.6%) with no. An additional 19 subjects rated the question with "I do not know" and were not considered in this analysis. Regarding the loudness hyperacusis question, 16 (9.9%) answered with never, 16 (9.9%) with rarely, 58 (36%) with sometimes, 27 (16.8%) with usually, and 44 (27.3%) with always.

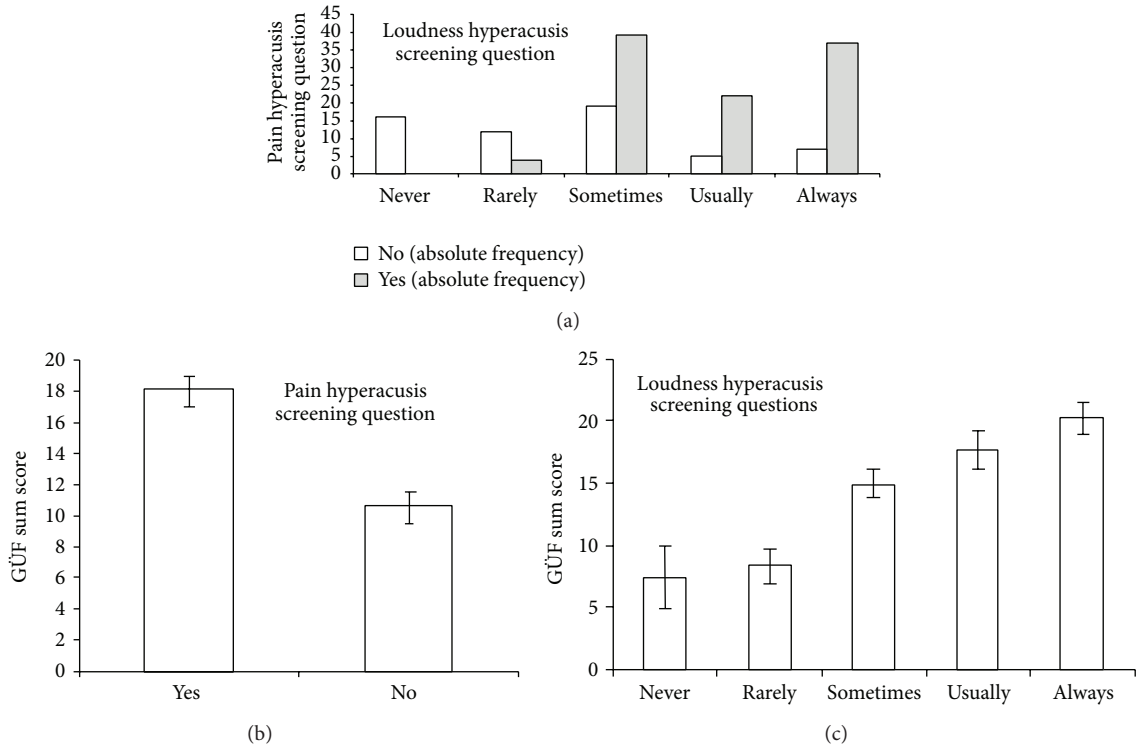


Figure 1: Association of pain and loudness hyperacusis screening question (a), of the GÜF (engl. hypersensitivity to sound questionnaire) sum score and pain hyperacusis screening question (b), and of the GÜF and the loudness hyperacusis screening question (c).

3.2. Correlation Analyses of Hyperacusis Scores. Association analyses are shown in Figure 1. The chi-square test showed a significant association of both screening questions ($\chi^2 = 50.147$; df = 4; $p < 0.001$). The higher the prevalence of loudness hyperacusis (from never to always) the higher the frequency of patients reporting pain hyperacusis, with "never" and "rarely" showing almost no positive pain hyperacusis answers. Pain hyperacusis was associated with increased GÜF scores (yes: 18.2 ± 8.1; no: 10.7 ± 9.3; $T = 5.385$; df = 159; $p < 0.001$) and loudness hyperacusis was positively associated with the GÜF score ($F = 11.089$; df = 4,156; $p < 0.001$) with no differences between the answers "never" and "rarely" ($p = 0.749$), a significant difference between "rarely" and "sometimes" ($p = 0.005$), no difference between "sometimes" and "usually" ($p = 0.149$), and no difference between "usually" and "always" ($p = 0.209$). The answers "never" and "rarely" differed from the other three answers (all p-values < 0.005), and the answer "sometimes" differed from "always" ($p = 0.001$). To sum up, patients reporting pain hyperacusis and at least "sometimes" in the loudness hyperacusis screening question seem to suffer from hyperacusis as identified with the GÜF.

We defined groups of tinnitus patients with and without hyperacusis based on these values (hyperacusis: pain hyperacusis = "yes" and loudness hyperacusis ≥ "sometimes") and calculated a linear discriminant analysis using the GÜF sum score as the independent variable. Wilks lambda was significant ($\lambda = 0.821$; $\chi^2 = 29.312$; df = 1; $p < 0.001$) meaning that 82% of the total (within and between groups) variability could not be explained by the group difference. For all the cases, 70.8% were classified correctly with sensitivity of 64.3% and specificity of 81.0%. The cut-off was at 14.59 GÜF sum score. Student's t-test between groups was significant (no hyperacusis: 10.71 ± 18.47; hyperacusis: 18.47 ± 8.00; $T = 5.683$; df = 159; $p < 0.001$).

3.3. Correlation Analyses on Item Level. On the item level both screening items were significantly (on a Bonferroni level) associated with GÜF items 3, 5, 6, 10, 13, and 14 which are associated with hearing problems and fear-related emotion or behavior such as withdrawal. Hearing related items 8 and 3 were highly associated with the loudness hyperacusis screening question, and earache item 11 was especially associated with pain hyperacusis (see Table 1).

Principal component analyses (PCAs; Table 1) with all GÜF and the two hyperacusis screening items fulfilled the statistical requirements (Kaiser-Meyer-Olkin measure: KMO = 0.901; Bartlett's test: $p < 0.001$). Factor one consisted of the GÜF items which were not associated with the screening items as indicated by t-contrasts and F-tests except for item 10 (anger about loud sounds). This factor represents problems or emotional distress related to reduced quality of daily life including family-related problems, ruined life, social withdrawal, and disturbed enjoyment of music amongst others. We name this factor "*quality of daily life*." Factor two consists of GÜF items which represent fear and fear-related behavior such as avoidance behavior of sounds, but also one earache item and the two screening items for pain

Table 1: Association of hyperacusis screening and questionnaire items.

	Pain hyperacusis screening question t-test (df = 159)	Loudness hyperacusis screening question F-test (df = 4,156)	Factor 1 loadings Quality of daily life	Factor 2 loadings Fear-pain hyperacusis	Factor 3 loadings Hearing-related problems
GÜF items					
(1) Fear of former not-disturbing sounds	$t = 2.854$; $p = 0.005$	$F = 3.240$; $p = 0.014$	0.411		(0.307)
(2) Worries to habituate	$t = 2.325$; $p = 0.021$	$F = 2.577$; $p = 0.040$	0.592 (0.575)		
(3) Problems to listen in environmental noise	**$t = 5.042$; $p < 0.001$**	**$F = 11.682$; $p < 0.001$**			0.759 (0.857)
(4) Social tensions with family	$t = 0.754$; $p = 0.452$	$F = 1.093$; $p = 0.362$	0.547 (0.419)		
(5) Sound avoidance	**$t = 9.706$; $p < 0.001$**	**$F = 16.703$; $p < 0.001$**		0.797 (0.479)	
(6) Fear of noise	**$t = 4.510$; $p < 0.001$**	**$F = 10.943$; $p < 0.001$**		0.594 (0.520)	
(7) Ruined life due to hyperacusis	$t = 1.257$; $p = 0.211$	$F = 2.261$; $p = 0.065$	0.810 (0.853)		
(8) Hearing problems in environmental noise	$t = 2.861$; $p = 0.005$	**$F = 6.028$; $p < 0.001$**			0.601 (0.653)
(9) Social withdrawal of others	$t = 1.242$; $p = 0.216$	$F = 0.695$; $p = 0.597$	0.572 (0.484)		
(10) Anger about loud sounds	**$t = 3.497$; $p = 0.001$**	**$F = 5.613$; $p < 0.001$**	0.508	(0.594)	
(11) Earache due to loud sounds	**$t = 4.475$; $p < 0.001$**	$F = 2.132$; $p = 0.079$		0.445 (0.398)	
(12) Daily life problems if problems persist	$t = 2.976$; $p = 0.040$	$F = 2.534$; $p = 0.042$	0.727 (0.628)		
(13) Withdrawal from loud sounds	**$t = 5.274$; $p < 0.001$**	**$F = 10.471$; $p < 0.001$**		0.616 (0.670)	
(14) Fear that sounds are damaging	**$t = 3.588$; $p < 0.001$**	**$F = 4.310$; $p = 0.002$**		0.533 (0.781)	
(15) Disturbed enjoyment of music	$t = 2.146$; $p = 0.033$	$F = 2.453$; $p = 0.048$	0.435		(0.335)
Screening questions					
Loudness hyperacusis	—	—		0.591	
Pain hyperacusis	—	—		0.653	

Bold font indicates significant effects corrected by Bonferroni (0.003 = 5%/15 contrasts per screening question). Numbers in brackets indicate factor loadings of patients with tinnitus and hyperacusis only.

Table 2: Association of hyperacusis factors with nonhyperacusis parameters.

	Factor 1 loadings Quality of daily life	Factor 2 loadings Fear-pain hyperacusis	Factor 3 loadings Hearing-related problems
Mean hearing level	$r = 0.184$; $p = 0.025$	$r = -0.052$; $p = 0.534$	**$r = 0.253$; $p = 0.002$**
THI	**$r = 0.499$; $p < 0.001$**	$r = 0.310$; $p < 0.001$	$r = 0.101$; $p = 0.201$
BDI	**$r = 0.426$; $p < 0.001$**	$r = 0.323$; $p < 0.001$	$r = 0.141$; $p = 0.098$
Quality of life: physical health	**$r = -0.361$; $p > 0.001$**	$r = -0.263$; $p = 0.001$	$r = -0.206$; $p = 0.009$
Quality of life: psychological health	**$r = -0.497$; $p < 0.001$**	$r = -0.312$; $p < 0.001$	$r = -0.159$; $p = 0.045$
Quality of life: social relationships	**$r = -0.351$; $p < 0.001$**	$r = -0.241$; $p = 0.002$	$r = -0.147$; $p < 0.063$
Quality of life: environment	**$r = -0.368$; $p < 0.001$**	$r = -0.195$; $p = 0.014$	$r = -0.162$; $p = 0.040$
TQ total score	**$r = 0.543$; $p < 0.001$**	$r = 0.316$; $p < 0.001$	$r = 0.204$; $p = 0.010$
TQ emotional subscore	**$r = 0.563$; $p < 0.001$**	$r = 0.340$; $p < 0.001$	$r = 0.088$; $p = 0.280$
TQ cognitive subscore	**$r = 0.560$; $p < 0.001$**	$r = 0.275$; $p = 0.001$	$r = -0.089$; $p = 0.280$
TQ intrusiveness subscore	**$r = 0.366$; $p < 0.001$**	$r = 0.287$; $p < 0.001$	$r = 0.211$; $p = 0.008$
TQ auditory subscore	$r = 0.258$; $p = 0.001$	$r = 0.327$; $p < 0.001$	**$r = 0.553$; $p < 0.001$**
TQ sleep subscore	**$r = 0.201$; $p = 0.011$**	$r = 0.052$; $p = 0.516$	$r = -0.119$; $p = 0.139$
TQ somatic subscore	**$r = 0.264$; $p = 0.001$**	$r = 0.181$; $p = 0.025$	$r = 0.190$; $p = 0.018$
Rating scale loudness	$r = 0.106$; $p = 0.179$	$r = 0.161$; $p = 0.041$	**$r = 0.202$; $p = 0.010$**
Rating scale discomfort	**$r = 0.180$; $p = 0.023$**	$r = 0.159$; $p = 0.046$	$r = 0.016$; $p = 0.845$
Rating scale annoyance	$r = 0.107$; $p = 0.177$	**$r = 0.232$; $p = 0.003$**	$r = 0.154$; $p = 0.051$
Rating scale ignorability	$r = 0.184$; $p = 0.020$	**$r = 0.222$; $p = 0.005$**	$r = 0.169$; $p = 0.032$
Rating scale unpleasantness	$r = 0.102$; $p = 0.198$	**$r = 0.222$; $p = 0.005$**	$r = 0.159$; $p = 0.044$

Bold font indicates the highest association within each external parameter; please note that quality of life is inversely coded explaining the inverse correlation coefficients.

and loudness hyperacusis. However, the loudness hyperacusis question asked about loud and also hurtful sounds. Thus, we call this factor "*fear-pain hyperacusis component*." The third factor is related to "*hearing difficulties*." PCA without the screening items showed the same factor structure except for item 10 (anger about loud sounds) which then was added to the factor "*fear-pain hyperacusis*" (Kaiser-Meyer-Olkin measure: KMO = 0.904; Bartlett's test: $p < 0.001$). Data of this PCA are not shown in Table 1. PCA without the screening items and including only hyperacusis patients (as defined by the screening items; see above; see Table 1) also showed a comparable factor structure except for items 1 (fear of former not-disturbing sounds) and 15 (disturbed enjoyment of music) which was added to the factor "*hearing problems*" and except for item 10 (anger about loud sounds) which was added to "*fear-pain hyperacusis*" (Kaiser-Meyer-Olkin measure: KMO = 0.832; Bartlett's test: $p < 0.001$).

3.4. External Validation of the Generated Hyperacusis Factors. We extracted the three factors with regression analyses and correlated the individual factor loadings with nonhyperacusis parameters to test for external validity (Table 2). The first factor "*quality of life*" was specifically associated with THI, BDI, and quality of life scales, the numeric rating scale discomfort, and the scores of all TQ subscales except for the auditory subscale. The second factor "*fear-pain hyperacusis*" was associated with the numeric rating scales: annoyance, ignorability, and unpleasantness. Factor three "*hearing-related problems*" was associated with the numeric rating loudness, the mean hearing level, and the auditory subscore of the TQ.

4. Discussion

It was recently demonstrated in a large worldwide sample of tinnitus patients that the prevalence of hyperacusis in chronic tinnitus is about 55% [9]. Hyperacusis was defined by the screening question "Do sounds cause you pain or physical discomfort?" which corresponds to "*pain hyperacusis*" according to the recent classification by Tyler and colleagues [2]. In the present sample which only included patients from the Tinnitus Center Regensburg (Germany) a similar prevalence of 63% was found. We defined the parameter "*loudness hyperacusis*" based on the classification of Tyler et al. [2] as the answer to the question "Do you have a problem tolerating sounds because they often seem much too loud? That is, do you often find too loud or hurtful sounds which other people around you find quite comfortable?" In our sample 19.8% of the patients answered "never" or "rarely," while 36% reported suffering from loudness hyperacusis "sometimes" and 44.1% "usually" or "always." The mean GÜF sum score in our sample was 2.4 points lower than in the original validation sample [4]. However the validation sample [4] consisted only of tinnitus patients reporting hyperacusis. The mean score of both samples was in the medium impaired

quartile of the GÜF (quartiles: light, medium, heavy, and very heavy). Prevalence of over 50% in our former and the present analysis and of about 40% in earlier studies [6] highlights a major role of hyperacusis in chronic tinnitus and the need for detailed assessment of this comorbid condition. This is particularly relevant because of the high need of therapy in this subgroup of patients with chronic tinnitus [9].

Since a detailed assessment of hyperacusis by specific questionnaires is not feasible in clinical routine, there is a need for validated screening questions. Based on this idea, we aimed at testing the suitability of the TSCHQ items for "*pain hyperacusis*" and "*loudness hyperacusis*" as screening questions for hyperacusis in chronic tinnitus. Indeed, both questions correlated significantly with the GÜF sum score, the here defined measure for hyperacusis. It turned out that the best cut-off for the five-point scale of loudness hyperacusis is between "rarely" and "sometimes" based on association of loudness hyperacusis with pain hyperacusis and the GÜF sum score (Figure 1). To conclude, both screening items might be helpful in screening tinnitus patients for hyperacusis.

On the other hand it turned out that most of variability of the group difference based on the GÜF sum score is not explained by only focusing on the screening items. After dividing the sample into groups with and without hyperacusis based on the two screening questions a discriminant analysis was calculated based on the GÜF sum score. With a cut-off of 14.59 GÜF scores Wilks λ and t-test between groups were significant; however 82% of variability is not explained at 71% correctly classified patients. This could be due to the multidimensional character of hyperacusis which cannot be fully identified with these measures. A further explanation may be that the screening items and the GÜF are measuring slightly different dimensions of hyperacusis.

The item-based analyses including t-tests, ANOVAs, and PCAs showed that both screening questions are associated with a factor which we defined as "*fear-pain hyperacusis*" which included items with fear-related and avoidance behavior content and pain-related items. One GÜF item regards earache, one screening item asks directly about pain, and one screening item asks about loud and hurtful sounds. Our findings confirm that the screening questions are mainly addressing fear- and pain-related mechanisms of hyperacusis in chronic tinnitus. It also implies that both screening questions addressing similar aspects of hyperacusis despite the different wording. Face validity is not fulfilled for these two questions, which might be related to the context of the data collection. The two hyperacusis questions are part of 35 questions about the tinnitus case history. Thus, even if these two questions are sensitive for the detection of hyperacusis and even if their wording refers to the two main aspects of hyperacusis (loudness and pain) they seem not to be sensitive enough to differentially detect the hyperacusis aspects "*hearing difficulties*" and "*quality of life*." This view is also confirmed by the high intercorrelation of both screening questions.

Beside fear-pain hyperacusis, other hyperacusis-related dimensions in chronic tinnitus were found to be associated with quality of daily life and hearing problems. The factor structure showed high external validity as shown by correlations with tinnitus-specific and tinnitus-unspecific parameters. Quality of life was associated with tinnitus, depressivity, and quality of life questionnaires. Hearing problems were related to mean hearing loss, tinnitus loudness, and the auditory subscore of the TQ. Fear-pain hyperacusis was related to annoyance, ignorability, and unpleasantness of tinnitus. Two conclusions can be drawn. First, patients with tinnitus, hyperacusis, and hearing loss cannot assign their hearing difficulties and their impaired quality of life specifically to one of the three conditions. This has to be considered in the interpretation of questionnaire scores. In other words, if a patient scores high in hearing difficulties in the hyperacusis questionnaire, hearing loss and tinnitus have to be considered as relevant confounding factors. Second, different dimensions of hyperacusis have also been postulated. An expert consensus suggested that loudness, fear, annoyance, and pain comprise hyperacusis [2]. The postulated annoyance dimension which is defined as "negative emotional reaction to sounds" manifesting as "irritation, anxiety, and tension" might be closely related to our fear-pain factor. The fear dimension of hyperacusis was thought to reflect avoidance behavior. Our analysis suggests that annoyance and fear hyperacusis are highly associated and can be represented in one dimension. Typically, anxiety disorders are associated with avoidance behavior as stated in the classification systems DSM 5 and ICD-10 [16, 17]. The role of anxiety and avoidance behavior in hyperacusis was recently corroborated [3]. The initial validation of the GÜF revealed the factors "cognitive reactions to hyperacusis," "actional/somatic behavior," and "emotional reaction to external noises" [4]. The hyperacusis questionnaire (HQ) showed three factors: attentional, social, and emotional [5]. To sum up, although the multiple dimensions of hyperacusis are not yet well understood, there is clear evidence for the factors fear, pain, and loudness. Components such as hearing problems, quality of life, cognitive and emotional reactions, and behavioral responses should be the focus of future studies.

5. Conclusion

We could demonstrate that the screening items of the TSCHQ are suitable to screen patients with chronic tinnitus for hyperacusis and are particularly sensitive for the hyperacusis-related aspects fear and pain. Our analyses revealed quality of life and hearing as further important dimensions of hyperacusis. In the assessment of the impact of hyperacusis on quality of life and hearing, tinnitus and hearing loss have to be taken into account as confounding factors.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

The authors wish to thank Sandra Pfluegl, Ulrike Stadler, and Helene Niebling for technical assistance.

References

[1] H. Aazh, D. McFerran, R. Salvi, D. Prasher, M. Jastreboff, and P. Jastreboff, "Insights from the first international conference on hyperacusis: causes, evaluation, diagnosis and treatment," *Noise and Health*, vol. 16, no. 69, pp. 123–126, 2014.

[2] R. S. Tyler, M. Pienkowski, E. R. Roncancio et al., "A review of hyperacusis and future directions: part I. Definitions and manifestations," *American Journal of Audiology*, vol. 23, no. 4, pp. 402–419, 2014.

[3] L. Blaesing and B. Kroener-Herwig, "Self-reported and behavioral sound avoidance in tinnitus and hyperacusis subjects, and association with anxiety ratings," *International Journal of Audiology*, vol. 51, no. 8, pp. 611–617, 2012.

[4] M. Nelting, N. K. Rienhoff, G. Hesse, and U. Lamparter, "The assessment of subjective distress related to hyperacusis with a self-rating questionnaire on hypersensitivity to sound," *Laryngo- Rhino- Otologie*, vol. 81, no. 5, pp. 327–334, 2002.

[5] S. Khalfa, S. Dubal, E. Veuillet, F. Perez-Diaz, R. Jouvent, and L. Collet, "Psychometric normalization of a hyperacusis questionnaire," *ORL*, vol. 64, no. 6, pp. 436–442, 2002.

[6] D. M. Baguley, "Hyperacusis," *Journal of the Royal Society of Medicine*, vol. 96, no. 12, pp. 582–585, 2003.

[7] S. Hébert, P. Fournier, and A. Noreña, "The auditory sensitivity is increased in tinnitus ears," *Journal of Neuroscience*, vol. 33, no. 6, pp. 2356–2364, 2013.

[8] M. Landgrebe, F. Zeman, M. Koller et al., "The Tinnitus Research Initiative (TRI) database: a new approach for delineation of tinnitus subtypes and generation of predictors for treatment outcome," *BMC Medical Informatics and Decision Making*, vol. 10, no. 1, article 42, 2010.

[9] M. Schecklmann, M. Landgrebe, B. Langguth et al., "Phenotypic characteristics of hyperacusis in tinnitus," *PLoS ONE*, vol. 9, no. 1, Article ID e86944, 2014.

[10] B. Langguth, R. Goodey, A. Azevedo et al., "Consensus for tinnitus patient assessment and treatment outcome measurement: Tinnitus Research Initiative meeting, Regensburg, July 2006," *Progress in Brain Research*, vol. 166, pp. 525–536, 2007.

[11] G. Goebel and W. Hiller, "The Tinnitus Questionnaire (TQ). A standardized instrument for grading the severity of tinnitus. Results of a multi-center study using the TQ," *HNO*, vol. 42, no. 3, pp. 166–172, 1994.

[12] R. S. Hallam, S. C. Jakes, and R. Hinchcliffe, "Cognitive variables in tinnitus annoyance," *British Journal of Clinical Psychology*, vol. 27, no. 3, pp. 213–222, 1988.

[13] C. W. Newman, G. P. Jacobson, and J. B. Spitzer, "Development of the tinnitus handicap inventory," *Archives of Otolaryngology: Head and Neck Surgery*, vol. 122, no. 2, pp. 143–148, 1996.

[14] World Health Organization, *The World Health Organisation Quality of Life (WHOQOL)—BREF*, World Health Organization, Geneva, Switzerland, 2004.

[15] M. Hautzinger, M. Bailer, H. Worall, and F. Keller, *Beck-Depressions-Inventar (BDI). Testhandbuch*, 2 Auflage Edition, Hans Huber, Bern, Switzerland, 1995.

[16] WHO, *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*, World Health Organization, Geneva, Switzerland, 6th edition, 1992.

[17] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, American Psychiatric Association, Washington, DC, USA, 5th edition, 2013.