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CLINICAL CHARACTERISTICS OF TINNITUS ANNOYANCE AND PERCEPTION

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ACADEMIC DISSERTATION

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To my family

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ABSTRACT

Tinnitus, or the perception of sounds without an external source, affects up to 15% of the adult population worldwide. It relates to a number of psychological and psychiatric disorders such as psychological distress, insomnia and depression, and develops on a broad range of physical insults. To date, it is nearly impossible to obtain quantitative data on this symptom and thus complaints are often labelled as 'only' imaginary. Nevertheless, the sheer number of affected individuals makes it clear that tinnitus is everything but an orphan symptom.

Variations in the clinical presentation may arise from the specific physical insult, the quality of first diagnosis and immediate medical aid as well as genetic predisposition. Thus, regional differences have to be considered when approaching tinnitus patients. The aim of this thesis was to study patient populations managed for tinnitus at the Department of Otorhinolaryngology – Head and Neck Surgery, Helsinki University Hospital (Helsinki, Finland). In the first study, we were able to show that music exposure even at low volume can pose a noise trauma and tinnitus occurs long before tone-audiometric hearing disabilities become evident. The alarming finding of the second study was its confirmation of pediatric tinnitus as a largely ignored symptom and that tinnitus in the childhood is under-diagnosed and this may have severe consequences for development of the individual. The third study could demonstrate that pupillometry can be considered as a viable option for studying autonomic activation in tinnitus subjects and emphasized the close link between tinnitus and depression. From our fourth study, a systematic literature review, we cannot clearly conclude if tinnitus and suicide are interrelated entities. The results of the last study indicate that tinnitus patients describe their own perceived tinnitus sound as well as external given sounds very divergent and therefore subjective tinnitus descriptions should be interpreted with great caution.

Taken together, an early recognition of tinnitus symptoms may increase not only the overall quality of life of the affected patients, more importantly, it may decrease the risk of psychological and psychiatric co-morbidities and suicidal behavior. A major limitation still is that tinnitus lacks both, clear-cut biomarkers that are specific enough to be allocated solely to the symptom and methods that are sensitive enough to detect them.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based upon the following publications:

I **Szibor A**, Hyvärinen P, Lehtimäki J, Pirvola U, Ylikoski M, Mäkitie A, Aarnisalo A, Ylikoski J. (2018)
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Clinical Characteristics of Troublesome Pediatric Tinnitus.
Clinical Medicine Insights Ear Nose Throat. 10:1179550617736521.
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III **Szibor A**, Lehtimäki J, Ylikoski J, Aarnisalo AA, Mäkitie A, Hyvärinen P. (2018)
Attenuation of Positive Valence in Ratings of Affective Sounds by Tinnitus Patients.
Trends in Hearing. 22(556), 233121651881621–10.
doi: 10.1177/2331216518816215

IV **Szibor A**, Mäkitie A, Aarnisalo AA. (2019).
Tinnitus and suicide: An unresolved relation.
Audiology Research, 9(1).
doi: 10.4081/audiores.2019.222

V **Szibor A**, Hyvärinen P, Mäkitie A, Aarnisalo AA. (2019).
Low inter-rater consistency in semantic profiles of tinnitus-like sounds rated by tinnitus patients.
Manuscript submitted

The publications are referred to in the text by their roman numerals.

ABBREVIATIONS

ABR	Auditory brainstem responses
AC	Auditory cortex
BDI	Beck's depression inventory
CS	Cochlear synaptopathy
DCN	Dorsal cochlear nucleus
DPOAE	Distortion-product otoacoustic emissions
EEG	Electroencephalography
fMRI	Functional magnetic resonance imaging
HHL	Hidden hearing loss
HR-QoL	Health-related quality-of-life
IADS	Affective digitized sounds database
IC	Inferior colliculus
IHC	Inner hair cells
MIHD	Music induced hearing disorder
MEG	Magnetencephalography
MGN	Medial geniculate nucleus
NAc	Nucleus accumbens
NIHL	Noise-induced hearing loss
OHC	Outer hair cells
PFL	Paraflocculus lobe
PTS	Permanent threshold shifts
PVCN	Posteroventral cochlear nucleus
SAM	Self-assessment manikin scale
SCL-90	Symptom check list 90
TFI	Tinnitus functional index
THI	Tinnitus handicap inventory
THQ	Tinnitus handicap questionnaire
TQ	Tinnitus questionnaire
TRN	Thalamic reticular nucleus
TRQ	Tinnitus reaction questionnaire
TSI	Tinnitus severity index
TSQ	Tinnitus severity questionnaire
TTS	Temporary threshold shifts
VAS	Visual analogue scales
vmPFC	Ventromedial prefrontal cortex
VNS	Vagus nerve stimulation
tVNS	Transcutaneous vagus nerve stimulation

1 INTRODUCTION

Tinnitus, or the perception of sounds without an external source, affects up to 15% of the adult population worldwide. It relates to a number of psychological and psychiatric disorders such as psychological distress, insomnia and depression, and develops on a broad range of physical insults. To date, it is nearly impossible to obtain quantitative data on this symptom and thus complaints are often referred to as 'only' fictional. But the high number of tinnitus sufferers make clear that tinnitus is everything but a rare symptom.

Variations in the clinical presentation may arise from the specific physical insult, the quality of first diagnosis and immediate medical aid as well as genetic predisposition. Thus, regional differences have to be considered when approaching tinnitus patients. We studied patient populations that over the years were managed at the Department of Otorhinolaryngology – Head and Neck Surgery, Helsinki University Hospital (Helsinki, Finland).

In a first study, we were able to show that music exposure even at low volume can pose a noise trauma causing tinnitus. Notably, tinnitus occurs long before tone-audiometric hearing disabilities become evident, a phenomenon previously coined as the 'hidden' hearing loss. Since hearing impairment is the ultimate fate of the affected, it is assumed that only early therapeutic interventions may initiate a recovery process. Studies to substantiate the major conclusions have been initiated aiming at both, the use of animal models to decipher underlying disease mechanisms and clinical studies searching for quantifiable disease correlates using different imaging techniques.

The most troublesome finding of the second study is its confirmation of pediatric tinnitus as a largely ignored symptom. The time between the first appearance of symptoms and a presentation in our clinic was slightly above 12 months. However, while adults reveal their symptoms and seek for medical aid, the suffering in the young remains largely unrecognized. This is likely due to the inability of children to properly describe their symptoms and a lack of recognition. As a consequence, however, tinnitus in the childhood is under-diagnosed, if not neglected, which unnecessarily delays proper therapies and affects the well-being of the young in a critical phase of their life's.

Recently, it was described that affective processing is altered in tinnitus patients and to a great extent characterized by emotional reaction to a phantom sound. Specifically, psychophysiological models and brain imaging studies have suggested a role for the limbic system in the emergence and maintenance of tinnitus. In principle, this makes tinnitus quantifiable. However, it remained unclear if the observed alterations are indeed tinnitus-specific or affect emotional processing in general. We have tested the valence and arousal of sounds from the International affective digitized sounds database (IADS) based on the normative valence ratings negative, neutral or positive in tinnitus patients. The individual autonomic response was measured simultaneously with pupillometry. Our findings suggest that affective processing is indeed altered in tinnitus patients and highlight a close link between tinnitus and depression.

As pointed out above, regional disparities have an impact on the development of tinnitus. Among all developed countries, Finland has one of the highest suicide rates. In 2013, the average mortality rate from suicide in Finland was 16.4 individuals per 100,000 as compared to 12.8 in countries organized in the Organization for Economic Co-operation and Development (OECD). This is in contrast to the overall positive perception of living conditions. Several studies investigated the link between tinnitus and emotional disorder without presenting conclusive results. We performed an in-depth analysis of the present literature and compiled a comprehensive review to sensitize affected and their families as well as clinicians. We identified 22 publications including original articles, case reports and reviews of which 10 fit our stringent search criteria. Most importantly, from the present studies it appears not feasible to univocally conclude on the co-incidence of tinnitus and suicide. This is due to methodological differences in these approaches, complex interrelations between tinnitus and other psychiatric comorbidities and confounding factors such as the inclusion of patients suffering from post-traumatic stress disorder. As a conclusion, we recommend concerted actions involving different medical disciplines reflecting the etiological heterogeneity of tinnitus and suicide to ultimately test for a causal relationship.

2 REVIEW OF THE LITERATURE

Tinnitus is a hearing disorder generally defined as the perception of a phantom sound perceived by the affected person in the absence of measurable external stimuli and may affect anyone at any time during the lifetime (Jastreboff, 1990). A distinction is made between the rare objective and the usual subjective tinnitus. The tinnitus is called objective if it is audible to another person. Reasons are pulsating blood vessels in the middle ear or inside the internal acoustic meatus or a myoclonus of middle ear or palatal muscles (Bhimrao et al., 2012). Subjective tinnitus is even audible only for the person concerned and cannot be measured acoustically. Suffers describe the sounds as ringing, hissing, static, crickets, screeching, whooshing, roaring, pulsing, ocean waves, buzzing, dial tones or music. Many patients experience more than one sound (Baguley et al., 2013). Tinnitus can be intermittent or chronic. Transient or reversible tinnitus typically does not need treatment and may have a different etiology. Very short transient tonal tinnitus, accompanied by fullness in the ear and transient mild hearing loss, is experienced by nearly everyone. Tinnitus can be localized to one or both ears, within the head or to an external point of origin (Baguley et al., 2013).Many tinnitus patients are not bothered by the sound and do not seek medical help. For others, it can impact on quality of life and cause debilitating problems such as depression, anxiety, frustration and insomnia (Nondahl et al., 2007) (Figure 1).

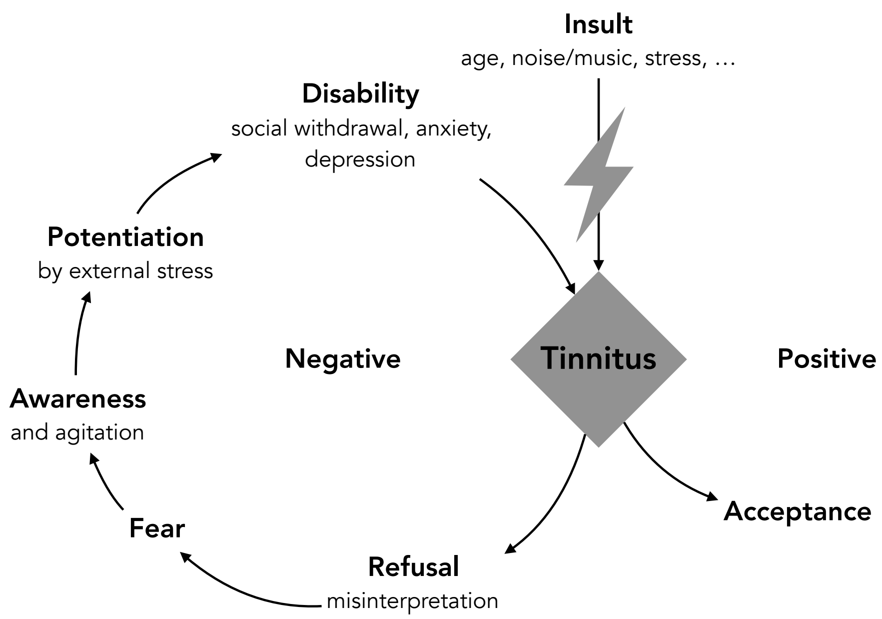

Figure 1: A vicious-circle model of tinnitus.

2.1 EPIDEMIOLOGY AND ETIOLOGY

Depending on the definition of tinnitus and the included criteria the prevalence rates in adult populations vary from 5.1% (Benson and Marano, 1998) to 42.7% (Gibrin et al., 2013). The prevalence of bothersome tinnitus ranged from 3.0% (Michikawa et al., 2010) to 30.9% (H.-J. Kim et al., 2015). Even comparing those studies that used the most common type of tinnitus question ('tinnitus lasting for more than five minutes at a time'), the prevalence varies widely from 11.9% (Fujii et al., 2011) to 30.3% (Sindhusake et al., 2003; McCormack et al., 2016). The prevalence of troublesome tinnitus increases with increasing age of the population (Al-Swiahb and Park, 2016; Nondahl et al., 2010). In general, it is assumed that the prevalence of tinnitus in children is equal to its prevalence in the adult population (Rosing et al., 2016). Although adults reveal their symptoms and seek medical help, suffering in young people is often undetected. This is due to both the inability of the children to exactly describe their symptoms and the lack of recognition.

Table 1: Known risk factors for the development of tinnitus and conditions associated with tinnitus symptoms (adapted from (Baguley et al., 2013)).

Risk factors/etiologies		**Diseases and/or conditions**
Cardiovascular disease		Hypertension
Endocrine and metabolic disorders		Diabetes mellitus, hormonal changes during pregnancy, hyperinsulinemia, hypothyroidism
Immune-mediated disease		Systemic lupus erythematosus, systemic sclerosis
Neurological diseases		Epilepsy, meningitis, migraine, multiple sclerosis
Orofacial disorder		Temporomandibular joint disorder
Otologic	infectious	Labyrinthitis, mastoiditis, otitis media
	labyrinthine	Ménière's disease, sensorineural hearing loss, vestibular vertigo
	neoplastic	Meningioma, vestibular schwannoma
	other	Impacted cerumen, noise, otosclerosis, presbyacusis
Ototoxic drugs		Analgesics, antibiotics, antineoplastic drugs, corticosteroids, diuretics, immunosuppressive drugs, non-steroidal anti-inflammatory drugs, steroidal anti-inflammatory drugs
Psychological conditions		Anxiety, depression, emotional trauma
Rheumatological disease		Rheumatoid arthritis
Traumatic events		Head or neck injury, loss of consciousness

The main risk factor for developing tinnitus is hearing loss (Nondahl et al., 2011), but not all patients with hearing loss reported tinnitus and not all tinnitus sufferers have hearing loss. Most often tinnitus is associated with noise-induced hearing loss (NIHL), but also co-occurs in patients with age-related hearing loss (presbycusis), Ménière's disease, and sudden deafness. Impacted cerumen in the ear canal, middle ear problems such as otosclerosis and otitis media, and other forms of hearing loss can also cause tinnitus.

Temporomandibular joint disorders and cervical spine disorders have been associated with the development or persistence of tinnitus (Bousema et al., 2018). Ototoxic medications can trigger tinnitus, such as salicylates, quinine, aminoglycoside antibiotics and platinum-based antineoplastic drugs (Dille et al., 2010). Also, obesity, smoking, alcohol consumption are risk factors (Nondahl et al., 2011). The bothersome nature of tinnitus has linked to an association with psychiatric conditions including depression and anxiety. Major depression has been described in up to 33% of patients with tinnitus and anxiety is also closely related and can be seen in up to 45% of patients with tinnitus (Zöger et al., 2006), while the lifetime prevalence for depression and anxiety disorder overall is about 10% (Lim et al., 2018; Somers et al., 2006)

Although tinnitus can result from many pathologies, excessive noise exposure is considered as the most prevalent cause of tinnitus (B. I. Han et al., 2009; Henry et al., 2005). However, in about 40% of patients no underlying etiology can be identified. In many patients, the emergence of tinnitus as a problem occurs long after the underlying medical condition. The trigger for the adverse or intrusive effects of tinnitus is sometimes unrelated to the associated condition (Henry et al., 2005).

2.2 PATHOPHYSIOLOGY

The pathology of tinnitus is complex and poorly understood (Møller, 2016). There is evidence about an interaction between peripheral pathologies and central auditory mechanisms (Noreña and Farley, 2013). The peripheral tinnitus has its cause in cochlear damage and the resulting changes in endocochlear potential leading to increased spontaneous cochlear activity. This hypothesis offers a possible explanation of different causes behind cochlear tinnitus (Noreña and Farley, 2013).

The reduced cochlear activity leads to a downregulation of inhibitory cortical processes and so to a hyperexcitability within the central auditory structures, including the primary auditory cortex (Noreña and Eggermont, 2003). But tinnitus is not just a straight forward correlate of the imbalance of firing patterns across the tonotopic array of the impaired cochlea, it can persist also after cutting of the auditory nerve (Baguley et al., 2013).

2.2.1 COCHLEAR PATHOLOGY

Cochlear damage may include loss of outer hair cells (OHC) electromotility, loss of synapses between inner hair cells (IHCs) and spiral ganglion neurons (synaptopathy), damage to the stereociliar bundle, death of OHCs or IHCs, or rupture of the basilar membrane. All these mechanisms lead to a decrease in neuronal output from the cochlea to the brain and they could count for the potential generation of compensation mechanisms in the brain (Chen and Fechter, 2003; Haider et al., 2018). Damage to these cochlear structures induce permanent threshold shifts (PTS), measurable by the pure tone audiogram, auditory brainstem responses (ABRs), or distortion-product otoacoustic emissions (DPOAEs). Audiometric hearing loss presumably caused by noise exposure or aging is present in most tinnitus sufferers (Roberts et al., 2008). However, not all tinnitus patients have abnormal audiograms. According to different studies more than 60% of people with tinnitus have with normal hearing capacity (Tucker et al., 2005). Animal data suggest that noise exposure or aging lead to a permanent loss of synapses between the IHCs and the cochlear nerve fibers (Kujawa and Liberman, 2015; 2009; Sergeyenko et al., 2013). This condition is called "hidden hearing loss" (HHL) (Schaette and McAlpine, 2011), associated with cochlear synaptopathy (CS) (Hickox and Liberman, 2014; Kujawa and Liberman, 2009). CS seems to increase the vulnerability of the cochlea to further traumatic stimulation (Chen and Henderson, 2009) and weaken or disturb central auditory processing, leading to poor sound discrimination and perceptual disorders such as tinnitus and hyperacusis (Alkharabsheh et al., 2017; Baiduc et al., 2013; Chen, 2018; Chen and Henderson, 2009; Schaette and McAlpine, 2011; Wan and Corfas, 2017). Most of our knowledge about CS are based on animal studies in mice and guinea pigs (Kujawa and Liberman, 2015; Lin et al., 2011). It seems, that humans are less susceptible to noise damage than smaller mammals (Dobie and Humes, 2017). The evidence for noise-induced CS in humans is poor and inconsistent. Only one study indicate a reduction in ABR wave I amplitude in tinnitus patients with normal audiogram (Schaette and McAlpine, 2011), however, this finding could not be reproduced by others (Gilles et al., 2016; Guest et al., 2017). More research is needed to understand the functional impact, prevalence, and ability to diagnose this condition in humans. It is not possible to say with certainty whether the findings of CS are the same in humans as showed in the animal models. Also, the temporary threshold shifts (TTS) animal models inducing a restricted CS may not be a particularly good model of the human case, where a mixed pathology involving synapses, inner and outer hair cells, and possibly other cochlear structures could all co-occur. The effects of CS on hearing could interact in a complicated manner with other forms of cochlear damage, and it is not yet clear whether these various forms of cochlear damage can be selectively diagnosed and characterized in clinic. Theoretical considerations have led to the hypotheses that CS leads to an impairment of tasks concerning temporal processing and/or listening in noise, and some evidence from human studies in this direction is beginning to emerge (Hickox et al., 2017).

2.2.2 CENTRAL MECHANISMS

The compensation mechanism occurring in the central nervous system during tinnitus is called "homeostatic plasticity" (Haider et al., 2018). Thereby the auditory neurons in the brain adjust their synaptic connections to maintain a neural network that is similar to that before the onset of peripheral damage. Neuronal correlates of tinnitus have been seen as neuronal hyperactivity in the posteroventral cochlear nucleus (PVCN), the inferior colliculus (IC), the dorsal cochlear nucleus (DCN) and the paraflocculus lobe of the cerebellum (PFL) (Cacace et al., 2014). Many studies support the theory, that the DCN is the induction site of tinnitus, from where it spreads to higher areas (Brozoski et al., 2002; Dehmel et al., 2012; Wu et al., 2016; Zhang and Kaltenbach, 1998). Other studies consider tinnitus as a result of neuronal hyperactivity in certain regions of the central auditory system, such as IC, cochlear nucleus and thalamus (Dong et al., 2010; Shore et al., 2016; Vogler et al., 2011).

Noise-induced tinnitus has been suggested to be related to increased neuronal hyperactivity in the auditory cortex (AC) at both acute (Hisashi Komiya Jos J Eggermont, 2009; Luo et al., 2017; Noreña and Eggermont, 2003) and chronic stages (Seki and Eggermont, 2003). and in some cases, lead to a reorganization of tonotopic maps in the AC (Robertson and Irvine, 1989; Salvi et al, 1990; Rajan and Irvine, 1998; Qiu et al, 2000; Syka, 2002; Noreña et al, 2003; Yang et al, 2007; Roberts, 2011; Yang et al, 2011).

2.2.3 NON-AUDITORY NEURONAL NETWORKS

Both animal studies and human neuroimaging studies (Elgoyhen et al., 2015) have confirmed tinnitus-related changes in nonauditory brain areas. Even if available neuroimaging studies show not all the same results, there is evidence that tinnitus is related to structural and functional alterations in prefrontal cortex, parietal cortex, cingulate cortex, amygdala, hippocampus, nucleus accumbens, insula, thalamus, and the cerebellum (Adjamian et al., 2014; Vanneste and De Ridder, 2012). Moreover, resting-state network measurements have disclosed prevalent connectivity changes in subjects with tinnitus compared to control groups. The modifications are interpreted as a compensation of the brain for the lack of auditory information from the cochlea. As cochlear damage results in a mismatch between expected auditory input and real auditory input, auditory memory and salience- and emotion-processing areas are reactivated (De Ridder et al., 2011; Elgoyhen et al., 2015). Following these hypotheses, the activation of the auditory cortex may reflect the loudness of the tinnitus, while the conscious perception of the tinnitus and the resulting distress are leading to the coactivation of different resting-state networks (De Ridder et al., 2014; Elgoyhen et al., 2015). Increased functional connectivity between the auditory cortices and the frontoparietal attention network in tinnitus patients has been shown in several EEG, MEG, and resting-state fMRI studies (Leaver et al., 2016; Schlee et al., 2009; Vanneste and De Ridder, 2015). Other studies have disclosed that tinnitus-related distress is associated with increased activity of the distress network and increased connectivity between auditory and stress-related brain areas (De Ridder et al., 2011; Vanneste et al., 2010; Carpenter-Thompson et al., 2015). However, there are a lot of individual differences in the involvement of the various overlapping brain networks, which can be an explanation for the clinical heterogeneity of tinnitus patients (De Ridder et al., 2014; Langguth et al., 2019).

2.2.4 MODELS OF TINNITUS PATHOPHYSIOLOGY

The data from different tinnitus studies can contribute to general pathophysiological models (De Ridder et al., 2014; Jastreboff et al., 1988; 1994; Rauschecker et al., 2010). Jastreboff et al. (Jastreboff et al., 1988) introduced the neurophysiological model of tinnitus, which resulted in the Tinnitus Retraining Therapy. In this model the auditory perceptual, emotional and reactive systems are involved in the genesis of tinnitus. After a short period of awareness of tinnitus-related activity, a process of habituation occurs, so that the activity is no longer consciously perceived. Although, in cases with negative emotional reinforcement described as fear, anxiety or tension, the limbic system and autonomic activation improve the activity and the perception persists.

The distinction between perception, behavioral and emotional reaction to tinnitus and the possibility for a feed-back loop between these processes was explicit. The Jastreboff model is widely accepted as a synthesis useful for patients, clinicians and researchers. While there is no empirical evidence to support this model, it is congruent with a modern understanding of the auditory system. A potential criticism is that the model does not represent the full complexity and dynamism of the human auditory system, but if the primary aim was to create a model of tinnitus that is easy to understand by patients then this may have been intentional (Baguley, 2002).

Rauschecker et al. (Rauschecker et al., 2010) proposed another tinnitus model based on the mechanism of noise suppression, in which subcallosal projections are involved in suppression of the tinnitus signal as sensory input at the thalamic level of brain processes. Functionally, the nucleus accumbens (NAc) and its correlated paralimbic circuitry were considered in the ventromedial prefrontal cortex (vmPFC), to show a crucial achievement in long-term habituation to persistent unpleasant noises. Sound-evoked neural activity is directed from the auditory periphery via the brainstem and thalamus (MGN: medial geniculate nucleus) to the auditory cortex (Ghodratitoostani et al., 2016). For emotional content evaluation of the sound, the same signal is conducted over the amygdala to the subcallosal area, which includes the NAc region and the vmPFC. The thalamic reticular nucleus (TRN) receives excitatory feedback projections from the subcallosal area and applies selective inhibition at the sections of the MGN corresponding to the unpleasant sound frequencies. This gain-control mechanism results in a highly specific filtering ("tuning out") of repetitive annoying noises, which do not reach conscious perception in the auditory cortex. As long as the NAc-system is intact the tinnitus signal is filtered out and will not be relayed to the auditory cortex. If the NAc-system becomes compromised it is no longer possible to cancel the tinnitus signal at the thalamic level and tinnitus perception results, and long-term reorganization of auditory cortex transfer the tinnitus to chronic.

The integrative model of the auditory phantom perception by De Ridder et al. (De Ridder et al., 2014) is a recent proposal, which conceive that tinnitus subnetworks incorporate neurophysiological model and noise canceling process. Minimal brain areas (auditory cortex, inferior parietal area, and ventromedial prefrontal/frontopolar cortex) are activated together to reach the conscious perception of tinnitus (Ghodratitoostani et al., 2016). The combination of functional neuroimaging and neuromodulation studies could provide some causal relationship between the acquired correlated networks. It has been suggested that tinnitus may be perceived as an emergent aspect of several dynamically overlapping subnetworks with different spontaneous oscillatory patterns and functional connectivity processing (Ghodratitoostani et al., 2016). The model hypothesized that the tinnitus core connects to other subnetworks via hubs and leads to bothersome effects such as mood disorders, distress, and lateralization.

2.3 MEASUREMENT OF TINNITUS

Tinnitus is manifold in forms and characteristics. However, tinnitus is not easily perceptible to others, and currently no objective measurements are yet established for the diagnosis of tinnitus. It is very difficult to assess the perceptual aspects of tinnitus for the suffers and the medical staff. The case history is of high importance for a correct diagnosis in all areas of medicine; especially for tinnitus, since it is basically a self-report phenomenon. The subjective nature of tinnitus is a problem not only in the clinical management of tinnitus patients, also for research applications. Measurements of tinnitus can be classified in subjective and objective.

2.3.1 SUBJECTIVE ASSESSMENT OF TINNITUS

Subjective measures of tinnitus include psychoacoustic tests (pitch match, loudness, masking ability), and psychological rating scales and questionnaires.

2.3.1.1 Psychoacoustic characteristics

The standard measurement of tinnitus pitch is tinnitus pitch matching. For pitch matching, the frequency of a tone is varied and the patient selects the tone that best matches the pitch of the tinnitus (Henry, 2016). Pitch matches for tinnitus occur often in the frequency region of maximum hearing loss or at the transition from normal to abnormal hearing (Eggermont and Roberts, 2004; Norena et al., 2002). Most typically, patients match their tinnitus to a tone above 3 kHz (Eggermont and Roberts, 2004). Pitch matches often vary over 2 to 3 octaves if measured in several sessions (Burns, 1984; Penner and Saran, 1994; Tyler and Conrad-Armes, 1983). Reasons are manifold, it could be that the patients have problems to the pitch matching itself; the tone used for matching may sound more like noise because of hearing loss (phenomenon of diplacusis, degraded pitch perception) (Burns and C. Turner, 1986); tinnitus experienced as a spectrum of sounds for most people and not as a pure tone (Norena et al., 2002; Roberts et al., 2008).

Tinnitus pitch matching is routinely used even though results are inconstant. The recommendation is to use multiple pitch masking be to identify the tinnitus frequency more accurate (McMillan et al., 2014). The most important dimension of tinnitus is its loudness (Henry, 2016). There are two common methods to assess tinnitus loudness: loudness matching and loudness ratings. Tinnitus loudness can be presented at hearing level (HL) or sensation level (SL), which is the level of tinnitus above hearing threshold (Andersson, 2003). Whereas dB HL reflects the level of the tone that is perceived as having the same loudness as the tinnitus (taken from the audiometer scale), dB SL is the difference between that measure and the hearing threshold at the same frequency (Hall et al., 2017). The loudness expressed in dB SL thus bring another source of subjective variability within this method. Tinnitus loudness is usually matched by a sound with a low SL, typically in the range 6-20 dB SL. (B. Moore, 2014) When loudness matches to tinnitus are made over a series of days, the matches can range up to 30-45 dB SL (Penner, 1983).

Whereas measures of tinnitus loudness and pitch try to quantify the tinnitus percept, minimum masking level (MML) measures the effect of sound on the perception of tinnitus (Henry, 2016). MML is the minimum level of broadband noise at which the patient's individual tinnitus is inaudible (Kostek and Poremski, 2013). It is a common method and regarded as correlating with the effectiveness of treatment (Jastreboff et al., 1994). For most patients tinnitus masking occurs up to 10dB SL (Henry et al., 2005). Broadband noise and the patient's hearing thresholds are used to define the MML. MML is an important measure of tinnitus subjective annoyance and acceptance of masking (Andersson, 2003; Vernon et al., 1990). A tinnitus sufferer best benefits from masking therapy when MML is close to the tinnitus loudness match (Vernon et al, 1990).

2.3.1.2 Questionnaires

Besides the psychoacoustical measurement, the effect of tinnitus on individual's quality of life is more important. These can be assessed by subjective outcome measurements such as questionnaires and rating scales. Questionnaires evaluate various aspects of daily life that can be influenced by tinnitus such as insomnia, concentration, annoyance, emotional distress and quality of life. There are several instruments in use for assessing level of severity of tinnitus complaints. In a review on disease-specific health-related quality-of-life (HR-QoL) instruments used to measure treatment outcomes in tinnitus trials, six different HR-QoL tinnitus instruments were identified (Kamalski et al., 2010).

The Tinnitus Handicap Inventory (THI; (Newman et al., 1996)) was developed to measure the impact of tinnitus on daily life. It consists of 25 questions split into three subscales; functional (12 items), emotional (8 items) and catastrophic (5 items). The functional and the emotional subscales show good internal consistency. But the unifactorial structure was criticized in some studies (Baguley and Andersson, 2003).

The Tinnitus Questionnaire (TQ; (Hallam et al., 1988)) was developed to measure tinnitus severity. The TQ includes scales for assessing emotional and cognitive distress, intrusiveness, auditory perception disorders, sleep disturbances and related somatic complaints (Adamchic et al., 2012). The 52 TQ items are internally consistent; but the subscales lack internal consistency (Cima et al., 2019).

The Tinnitus Reaction Questionnaire (TRQ; (Wilson et al., 1991)) was developed to assess the psychological distress associated with tinnitus. The 26 items have four subscales: general distress, interference, severity, and avoidance of the tinnitus.

The Tinnitus Severity Index (TSI; (Meikle et al., n.d.)) was introduced as a measure of how much tinnitus negatively impacts a patient's life and how annoying patients perceive their tinnitus. Eleven items specifically measure how much tinnitus interferes with everyday life.

The Tinnitus Handicap Questionnaire (THQ; (Kuk et al., 1990)) was intended to measure patients perceived degree of handicap due to tinnitus. The THQ has three domains physical health/emotional status/ social consequences, individual hearing and communication difficulties, and patient's personal view on tinnitus. This questionnaire is useful for objectifying the impact of tinnitus on the patient's life and provides data that define the handicap result from tinnitus. This questionnaire assesses large areas of tinnitus affections, and, by using broad scale (ranging from 0 to 100) provides better sensitivity and the potential to detect even small changes in the treatment and assessment process (Arian Nahad et al., 2014).

More recently, the Tinnitus Functional Index (TFI; (Meikle et al., 2012)) was developed as a new measure of the severity and negative impact of tinnitus, both for use as a diagnostic tool and for measuring treatment-related changes in tinnitus. Using exploratory factor analysis, the tinnitus domains were divided into eight different subscales: intrusiveness, sense of control, cognition, sleep, auditory, relaxation, quality of life, and emotional distress.

The TQ and the THI are widely used in clinical practice and clinical trials (Hall et al., 2016). Additionally, almost all existing clinical practice guidelines (Fuller et al., 2017) recommend using the Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983) to assess negative affect related to tinnitus (Cima et al., 2019).

A patient can also indicate the experienced annoyance and loudness on a rating scale. There are different methods of rating scales, for example Numeric Rating Scales, Visual Analogue Scales (VAS) and Verbal Rating Scales (Rabau et al., 2015). One of the most used method is the visual-analogue scale (VAS), regularly applied to assess chronic pain. In tinnitus patients, the patients are asked to assign a 0 to 10 score to their tinnitus. The assessment must be carried out in relation to volume and disturbance. It is easily applicable and understood by most patients. Like psychoacoustic measures, rating scales can be used to evaluate rapidly acting tinnitus treatments as they require very little time for the respondent to register a response. And, like psychoacoustic measures, there is little or no information concerning their responsiveness to treatment-related changes in tinnitus.

2.3.2 OBJECTIVE ASSESSMENT OF TINNITUS

Although several audiological, radiological and physiological tests evaluating abnormalities in peripheral and central auditory organs of sensorineural tinnitus are available, until now, no routine measurement to objectively verify tinnitus exists.

The auditory brainstem response (ABR) has been extensively studied over the last years with the hopes of finding possible abnormalities related to the pathology. In a review of 22 related articles (Milloy et al., 2017) no significant differences in amplitude and latency between tinnitus and controls were found. Nonetheless, the longer latency and reduced amplitude of wave I was most consistent in the tinnitus group with normal hearing compared to matched controls (Milloy et al., 2017).

Otoacoustic emissions (OAE) are sounds released from the outer hair cells of the cochlear, either spontaneously or in response to an evoked stimulus. One popular theory is that tinnitus may originate from damaged OHC within the cochlear and therefore direct measurement of these emissions could be used to identify the presence of tinnitus. But an absence or reduction in the suppression of OAEs may also occur in other cases of retrocochlear diseases, like auditory neuropathy, acoustic neuroma and impaired auditory processing (Geven et al., 2011). So far, people with normal hearing and tinnitus have significantly more abnormal results of OAE than people with normal hearing without tinnitus (Granjeiro et al., 2008). It seems that OHC dysfunction detectable by OAE are not sufficient to diagnose tinnitus.

fMRI is a noninvasive radiological method to correlate changes in brain activity with local blood oxygenation. It can be repeatedly administered without dose limitation to spatially map the brain activation of the auditory cortex and the signaling pathway (Melcher et al., 2000). There are only two studies using fMRI as an objective test for tinnitus with divergent results. Melcher et al. (Melcher et al., 2000) found differences in IC activity in subjects with unilateral tinnitus while Gopal et al. (Gopal et al., 2017) found no differences between tinnitus and non-tinnitus groups. Both studies were limited by their small sample size (n=24 and n=14 tinnitus patients, Melcher et al. and Gopal et al., respectively), while the applicability and availability of using MRI machines on a larger scale would have to be considered.

2.4 COMORBIDITIES OF TINNITUS

Several studies have shown that chronic tinnitus is highly associated with psychological comorbidities (Pattyn et al., 2015; Salviati et al., 2014; Zirke et al., 2013a). Common conditions include insomnia, concentration problems, depression, or anxiety disorders that can lead to social isolation and even to lose their ability to pursue regular work. Depression and anxiety disorders are the most common mental disorders in tinnitus (Malakouti et al., 2011; Sahlsten et al., 2018); but tinnitus can also be associated with obsessive–compulsive disorder (Folmer et al., 2008)[7], somatoform disorders (Leaver et al., 2015), eating disorders (Malakouti et al., 2011), and ineffective coping strategies (Zirke et al., 2013b). Tinnitus is often accompanied by hyperacusis (Baguley, 2003), a lowered tolerance for sounds. It affects all kinds of sounds and may cause more distress than the perception of the tinnitus (Jastreboff, 1990).

2.4.1 TINNITUS AND DEPRESSION

Symptoms of depression are common in patients with tinnitus, and there is an overlap between the factors associated with depression and with tinnitus, such as insomnia and anxiety (Durai and Searchfield, 2016; Langguth et al., 2011).

Several studies have investigated the rates of depression amongst people with tinnitus, but the reported frequencies vary widely. Most of the studies have used self-report symptom questionnaires, such as Beck's Depression Inventory (BDI) or the Symptom Check List 90 (SCL-90). These questionnaires were developed for screening psychiatric symptoms and follow-up on symptom severity during treatment and are not validated for diagnostic evaluation. The reported prevalence ranges from 28% (Trevis et al., 2016), 25.6% (Bhatt et al., 2017), 41.7% (Kehrle et al., 2016) up to 78% (Sullivan et al., 1988).

More accurate psychiatric diagnoses are obtained by the use of a structured diagnostic interview, like the Structural Clinical Interview for DSM-IV disorders (SCID) (First et al., 1997). These interviews indicate that 60–78% of tinnitus patients have at least one lifetime psychiatric disorder (Malakouti et al., 2011; Zöger et al., 2001) and 32.5–77.5% have lifetime depression (Malakouti et al., 2011; Sullivan et al., 1988).

In a systematic review on the evidences of an association between tinnitus and depression (Geocze et al., 2013) three possibilities of associating depression and tinnitus were postulated: depression affect tinnitus, tinnitus predisposing individuals to depression, and tinnitus appear as a comorbidity in patients with depression.

2.4.2 TINNITUS AND ANXIETY

Anxiety belongs to the most basic physiological emotions of human beings and may be part of almost every psychiatric disease. The lifetime prevalence for anxiety disorders overall is about 10% (Somers et al., 2006). Anxiety is even more frequent in individuals with tinnitus. Various studies reported anxiety in 10% (Bartels et al., 2008) up to 95% (Trevis et al., 2016).

People with anxiety disorders suffer unnecessary or have a disproportional apprehension or fear (Schuurmans and van Balkom, 2011). The third edition of the Diagnostic and Statistical Manual of Psychiatric Disorders (DSM III, APA, 1980) defined several specific anxiety disorders such as panic disorder, agoraphobia, social anxiety, posttraumatic stress syndrome (PTSD), obsessive-compulsive disorder, and generalized anxiety disorder.

2.4.3 TINNITUS AND INSOMNIA

Insomnia is the second most frequent comorbidity in tinnitus patients (Asplund, 2003) with a prevalence up to 77% (Aazh and B. C. J. Moore, 2019; Schecklmann et al., 2015), but the mechanisms underlying the association between tinnitus loudness and sleep disturbances remain unclear. Tinnitus loudness is a main aspect of tinnitus but it is not clear whether the degree of insomnia is directly related to tinnitus loudness or whether the degree of insomnia is related to psychological factors such as annoyance that are themselves related to tinnitus loudness (Aazh and B. C. J. Moore, 2019). Folmer and Griest (Folmer and Griest, 2000) reported that insomnia is associated with greater perceived loudness and severity of tinnitus. But they did not consider the effect of other factors known to be related to insomnia, such as depression, anxiety, cardiovascular disorders, and pain (Jansson-Fröjmark et al., 2012). In a mediation analysis by Aazh and Moore (Aazh and B. C. J. Moore, 2019) no direct relationship between tinnitus loudness and insomnia was found. They concluded that this relation is mediated via depression, tinnitus handicap and tinnitus annoyance.

Most studies on tinnitus and insomnia analyze just the sleep items included in tinnitus questionnaires (Alster et al., 1993; Fioretti et al., 2013; Folmer and Griest, 2000), only a few studies applied insomnia specific questionnaires that included psychological and cognitive variables (Crönlein et al., 2007; Miguel et al., 2014; Schecklmann et al., 2015).

3 AIMS OF THE STUDIES

The early recognition and proper management of tinnitus increase not only the overall quality of life of the affected patients, most importantly, it will decrease the risk of psychological and psychiatric co-morbidities and even suicide behavior. So far, tinnitus lacks objective biomarkers that are specific enough to be allocated solely to the symptom and methods that are sensitive enough to detect them. There is a lot of variation in the clinical presentation, and thus, regional differences have to be considered when approaching tinnitus patients. We studied Finnish patient populations that had been managed by ENT specialists in Helsinki, Finland.

Our specific aims were:

Study I

To record and analyze retrospectively clinical and psycho-physical characteristics of MIHD in individuals who had experienced a single trial of acoustic overstimulation from music.

Study II

To study retrospectively children having troublesome tinnitus in order to identify suspected triggers for tinnitus and accompanying morbidities.

Study III

To measure and quantify prospectively deviations in affective processing in patients suffering from tinnitus using behavioral and physiological parameters.

Study IV

To review available reports on the prevalence of suicide and suicidal behavior with tinnitus patients in order to collate current concepts and to identify possible alarming signs and risk factors.

Study V

To study prospectively how tinnitus patients perceived their tinnitus sound.

4 PATIENTS AND METHODS

4.1 PATIENTS

Ethical considerations

The design of studies I and II required no Research Ethics Board approval as these were based only on patient charts. Data were collected retrospectively, and the studies had no impact on ongoing treatment decisions. Institutional research permission was granted.

All parts of the studies III and V were approved by the Research Ethics Board at the Helsinki University Hospital and conducted in line the Declaration of Helsinki (7th revision 2013). Prior to enrollment, each participant received written and oral information on the study and signed a consent form.

No segregation of cases was made on the basis of audiometric results or sociodemographic variables.

Study I

Data on clinical and psychophysical characteristics of 104 consecutive outpatients presenting to the Helsinki Tinnitus Clinic (Helsinki, Finland) from January 2010 to March 2014 were analyzed retrospectively. The patient population consists of 71 males and 33 females with an age ranging from 14 to 62 years. The major inclusion criterion was tinnitus triggered by an exposure to loud music within three months before the first visit. Specific exclusion criteria were: time delay more than 100 days from the traumatic exposure; presence of otologic or neurologic diseases prior to the noise trauma; and history of vertigo or dizziness.

Study II

A series of 5768 patients who had been managed for tinnitus complaints at the Department of Otorhinolaryngology – Head and Neck Surgery at the Helsinki University Hospital between 2010 and 2015 with tinnitus complaints were retrospectively screened. Among them we identified 112 children under the age of 19 years. The cohort consists of 45 girls and 67 boys. All patients had troublesome tinnitus that had led to a referral and consequent visit to our institution. No segregation of cases was made on the basis of audiometric results or socio-demographic variables.

Study III

Ten tinnitus patients participated in this prospective study between May and September 2017. All participants were patients at the Hearing Center at the

Department of Otorhinolaryngology – Head and Neck Surgery, Helsinki University Hospital (Helsinki, Finland) and had been referred to the Hearing Center by general practitioners because of bothersome tinnitus. All patients had undergone standard audiological evaluation by an ENT specialist prior to participating in this study.

Study V
In this study 26 patients participated between December 2017 and May 2018. All participants were patients at the Department of Otorhinolaryngology – Head and Neck Surgery, Helsinki University Hospital, Helsinki, Finland and had been referred to the Hospital by general practitioners because of bothersome tinnitus. All patients had gone through standard audiological evaluation by an ENT specialist before participating in this study.

4.2 AUDIOLOGICAL EXAMINATIONS

Study I, II and V
All patients underwent standard audiological examination including pure tone-audiometry for frequencies ranging from 125 Hz to 12.0 kHz for both ears. Clinical audiometers and earphones (Interacoustic AC 40 and Telephonics TDH 39 P) generated and reproduced the acoustic signals in a sound-proof chamber. The audiometer was calibrated according to ISO 8253-1:2010 standard (International Organisation for Standardization 2010). TDH 39 P headphones were used and calibrated according to IEC 60318-3:2014 standard (International Electrotechnical Commission 2014).

Study I
Psychoacoustic pitch and loudness matches were determined for each patient.

4.3 PSYCHOPHYSICAL EVALUATIONS

Study I, III, V
Tinnitus severity was evaluated using the THI. The THI is a self-report 25-item questionnaire with three answer possibilities (no; yes; sometimes) that yields highly reliable scores ranging from 0 to 100. It is one of the most commonly used questionnaires to quantify the impact of tinnitus on daily life. There exist no validated THI questionnaire in Finnish. The original English version was translated into Finnish to be used in these studies. The Finnish version was back translated into English to exclude incorrectness in translation. The THI score was calculated according to the original questionnaire (yes=4, sometimes=2, no=0).

Study I
Tinnitus loudness and annoyance were characterized using the visual analogue scale (VAS), which is a measurement instrument for purely subjective symptoms. Awareness of tinnitus is given in percentage (0–100%).

4.4 SOUND STIMULI

Study III
Sounds from the IADS-2 database (Bradley and Lang, 2007; Stevenson and James, 2008) were used in the study. Sixty samples were chosen in three affective categories based on the normative ratings of the sounds. The three categories were: negative, positive and neutral. Sounds were presented at a comfortable level via Audio Technica ATH-M50x professional circumaural monitor headphones connected to the headphone output of an Apple MacBook Pro.

Study V
The experiment was implemented on an iPad mini tablet computer (Apple Inc., CA, USA), and the sounds were played through Audio Technica ATH-M50x professional circumaural monitor headphones connected to the headphone output of the tablet. The RMS amplitudes of the sounds were A-weighted, but the overall presentation level was not controlled; subjects could control the sound volume so that they could hear the sounds clearly at a comfortable level. They were also able to indicate if they could not hear the sound.

The sounds used in the experiment were:

1. 125 Hz tone
2. 125 Hz tone amplitude modulated at 10 Hz
3. 1 kHz tone
4. 1 kHz tone amplitude modulated at 10 Hz
5. 8 kHz tone
6. 8 kHz tone amplitude modulated at 10 Hz
7. 16 kHz tone
8. 16 kHz tone amplitude modulated at 10 Hz
9. 1/3-octave-band noise centered at 125 Hz (111 Hz – 140 Hz)
10. 1/3-octave-band noise centered at 125 Hz (111 Hz – 140 Hz) amplitude modulated at 10 Hz
11. 1/3-octave-band noise centered at 1 kHz (891 Hz – 1122 Hz)
12. 1/3-octave-band noise centered at 1 kHz (891 Hz – 1122 Hz) amplitude modulated at 10 Hz
13. 1/3-octave-band noise centered at 8 kHz (7127 Hz – 8980 Hz)

14. 1/3-octave-band noise centered at 8 kHz (7127 Hz – 8980 Hz) amplitude modulated at 10 Hz
15. 1/3-octave-band noise centered at 16 kHz (14254 Hz – 17959 Hz)
16. 1/3-octave-band noise centered at 16 kHz (14254 Hz – 17959 Hz) amplitude modulated at 10 Hz

4.5 EXPERIMENTAL PROCEDURE

Study III

Eye Tracking:

Pupil diameter, expressed in number of raw pixels, from both eyes was recorded with a head-mounted SMI 3D VOG eye tracking system at a sampling rate of 50Hz. Eye tracking was performed continuously throughout the experiment, along with the below-described experimental procedures.

The participants were seated in an upright position in front of a computer monitor. The auditory stimuli and visual instructions were presented using the PsychoPy toolbox (Peirce, 2007) running on an Apple MacBook Pro, to which the external monitor and keyboard for response collection were connected (Figure2).

For each individual sound, the following trial structure was carried out:

- A text "Get ready for the next sound" was shown on the monitor for 3 s.
- A fixation cross was shown in the middle of the monitor.
- After 4 to 6 s the sound sample was played.
- The fixation cross was shown up to 5 s after the end of the sound.
- A valence self-assessment manikin (SAM) scale (Bradley and Lang, 1994) was shown and the participant was asked to enter their value rating from 1 to 9.
- An arousal SAM scale was shown, and the participant was instructed to enter their value rating from 1 to 9.
- A blank screen was shown for 3 s before moving to the next trial.

The experiment was split into two separate blocks, both containing 30 sounds from each category.

During one of the blocks, the participant received transcutaneous vagus nerve stimulation (tVNS), administered to the left tragus at a level exceeding the tactile threshold but below nociceptive threshold. tVNS was applied to study if it affects pupil reactions, i.e. constriction and/or dilation, upon sound exposure. There was no electrical stimulation in the other block. The block in which tVNS was applied was chosen randomly for each subject.

Figure 2: Trial arrangement for the eye tracking and sound presentation (photograph taken by Mika Vuoto).

Study V

For each participant the following structure was employed:

- the participants were shown a pre-determined list of adjectives that have been used to describe tinnitus sounds in Finnish tinnitus questionnaires. Next to each adjective was a slider control, which the participants used for indicating how well the related adjective described their own tinnitus sound. The left extreme of the slider corresponded to "Does not describe my tinnitus sound at all", and the right extreme of the slider corresponded to "Describes my tinnitus sound perfectly".
- the participants listened to continuous synthesized sounds. Their task was to use the same adjectives and slider controls as in step 1 and rate how well the adjectives described the synthesized sounds. In addition, they rated how similar the synthesized sound was to their tinnitus sound using a slider control. The left extreme of the slider corresponded to "Not at all like my tinnitus sound" and the right extreme of the slider corresponded to "Identical to my tinnitus sound". Participants listened to the sounds in a randomized order.

There were no intermediate visual markers on the slider scales. The slider positions were internally converted to a value from 0 to 100, but this value was not shown to the participants.

4.6 STATISTICAL ANALYSIS

The statistical analyses were performed using IBM SPSS statistics, Version 22 (SPSS Inc., Chicago, USA). The data are reported as mean ± standard deviation (SD). All tests were performed as two-sided with the significance level set at 0.05.

Study III

For each response, the subject's own SAM rating was subtracted from the normative value from the IADS-2 database to get a measure of deviation from normative values.

Pupil size time series was averaged across both eyes, after which the signal was smoothed using a 15-sample median filter. Trials with more than 20% of blinking were rejected and not included in further analysis. As a final preprocessing step, pupil dilation was expressed as a relative value with respect to the average of a 2-s baseline period prior to sound onset. Pupil responses were compared across the three sound categories by calculating an average dilation between 2- and 8-s after stimulus. For each subject, the averaging was performed across time and across all sounds in belonging to the same category, in total resulting in three values for each individual. Pairwise t tests were performed between the different categories to test the null hypothesis that the average pupil dilation did not differ between sound categories, and the alternative hypothesis being that the pupil responses would be larger or smaller depending on the sound category.

Study V

The slider positions were converted to an integer value from 0 to 100. For each presented sound, this resulted in a rating profile with 18 values corresponding to the different adjectives. As a first analysis step, the highest-ranked adjective was determined for each sound. This approach was thought to provide roughly similar results as would a task, where the participant would be asked to pick one adjective that best describes the sound. The consistency between individual participants' rating profiles of the same sound was assessed using intra-class correlation with a two-way random, single score ICC(C,1) model, where each participant was treated as a rater, and each adjective was treated as a rating unit.

Another option of analyzing the intra-individual consistency in ratings is to look only at a single adjective at a time and treat each sound as a subject, again taking individual participants as raters. Here, Krippendorff's alpha was used as a measure of inter-rater reliability, due to the fact that each rater (participant) possibly rated only a random subset of the units (sounds).

4.7 LITERATURE REVIEW

Study IV

A comprehensive systematic literature search was performed in PubMed, Ovid, and Cochrane databases using the following search terms: ("tinnitus"[MeSH Terms] OR "tinnitus"[All Fields]) AND (("depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields]) OR "depressive disorder"[All Fields] OR "depression"[All Fields] OR "depression"[MeSH Terms]) AND ("suicide"[MeSH Terms] OR "suicide"[All Fields])).

5 RESULTS

5.1 MUSIC INDUCED HEARING DISORDERS

Of the patients included, 87.5% presented within 30 days (range 5–91 days) from the acoustic overstimulation from music. Two-thirds of the affected were male. The traumatic exposure had occurred in concerts (41%) or nightclubs (31%), during band playing (21%), using headphone (4%) or during studio work (2%). Tinnitus was experienced most often (78%) as a high frequency tone such as whining, ringing, beeping, whistling or TV-tuning sound at 6.0kHz (n=13), 8.0kHz (n=26), 10.0kHz (n=25) and 12.0kHz (n=17). The sound level of tinnitus-matched tones (n=90) was relatively low. In 21% of the cases, tinnitus was matched to a tone higher than 30dB (HL). The severity of the tinnitus was scored using THI. The scores ranged from 0 to 94 (average ± SD, 43.1 ± 22.8). The majority reported of mild (26%) or moderate (29%) symptoms, and all others complained of slight (13%), severe (15%) or catastrophic tinnitus (9%).

Relevant comorbidities were sleeping disorders (71%), concentration disorders (40%) and anxiety disturbances (40%). Hyperacusis was present in 65%.

It was one of the major aims of this study to relate subjective hearing dysfunctions with detectable loss of hearing thresholds. Unexpectedly, hearing as measured by pure-tone audiometry was normal in 60% of the patients, 31% had a (chronic) high frequency and 9% a mild low frequency hearing loss. None of the patients reported acute hearing loss at the time of the examination, but two had been diagnosed with temporary threshold shift immediately after the music trauma.

In order to correlate the THI scores with subjective perception, tinnitus was rated similar to VAS (from 10 to 100). The values (average ± SD) for loudness, annoyance and awareness were 42.4 ± 19.4, 54.2 ± 23.6 and 60.3 ± 24.7, respectively. VAS values and awareness correlated strongly with THI scores ($p < 0.001$ each). However, no clear correlation was found when the THI scores were correlated with hearing loss. The finding that 68 (65%) patients reported symptoms of hyperacusis prompted us to quantify the hyperacusis occurrence in the different severity classes of tinnitus. As expected, higher THI scores increased the probability of suffering from hyperacusis dramatically. With THI scores describing slight, mild or moderate tinnitus it is 1.3–2.5 times more likely to develop hyperacusis. With severe or catastrophic tinnitus, the ratio increases to 8–13.

5.2 TINNITUS IN CHILDREN

The age of all children reporting to clinic with suspected tinnitus ranged from 6 to 18 years (average ± SD 14.4 ± 2.9). The tinnitus was classified idiopathic in the absence of a disease-related trigger in the patient's clinical history when presenting with first symptoms in 15%. However, 14% had experienced a noise trauma, 12% had a history of middle ear infection, 4% reported a preceding viral infection, one patient suffered from an earlier basilar skull fraction, and 16% of the children had undergone orthodontic treatment, another 12% showed muscular neck tension, and 9% showed various psychological disorders.

In 58% of the cases, the tinnitus was bilateral while an isolated right or left side involvement was seen in 24% and 18%, respectively. Tinnitus was almost exclusively described as continuous high-frequency tone (96%). Only 5 children reported of a pulsatile quality. A diagnostic MRI of the brain in these patients revealed no pathological abnormalities of the vascular pattern.

The hearing capability was measured by pure-tone audiogram. There are different approaches to define hearing loss. We classified hearing capability as normal if hearing loss was less than 25 dB at one or several frequencies or according to the pure-tone average (80% of all cases).
Only 23 patients presented a clinically relevant hearing loss. In all, 21 had a sensorineural and two a conductive impairment. 20 patients had unilateral and only 3 patients bilateral hearing loss. Typical co-morbidities were observed such as sleeping disorders in 38%, concentration disorders in 12% and hyperacusis in 9% of the cases. Of note, children experienced a delay of roughly 12 months from first symptoms to presentation at our clinic.

5.3 AFFECTIVE PROCESSING IN TINNITUS PATIENTS

Subjective ratings of the sounds by tinnitus patients differed significantly from the normative ratings. For positive sounds, both valence and arousal were below normative values. In negative and neutral sounds, only arousal ratings were lower than normative values.

The pupillometry data show that negative sounds elicited a greater mean dilation during *2–8 s*, compared to neutral ($t = 4.4, p < 0.01$) and positive sounds ($t = 2.4, p < 0.05$). No significant difference was found between responses to neutral and positive sounds.

5.4 TINNITUS AND SUICIDE

Search results

We identified a total of 22 reports that conformed to our search terms in three public databases, i.e. PubMed, Ovid, and Cochrane (for details please refer to Patients and Methods). The abstracts of all reports were evaluated carefully leaving 10 reports eligible for further analysis based on predefined inclusion criteria. Overall, we identified three types of articles: prevalence studies, case reports and review articles.

Prevalence studies

We found five prevalence studies. Vogel et al. (Vogel et al., 2014) conducted a survey among 943 students in Dutch inner-city senior-secondary vocational schools in 2014 with the aim to study music-related hearing impairments. The students answered questionnaires about their sociodemographic background, music listening behaviors and health. Indeed, 10% of the students reported permanent hearing-related symptoms like tinnitus, muffled sounds, distortion, hyperacusis or hearing loss. One query related at the mental health status was: "*I often or very often seriously thought to end my life during the past 12 months. (yes/no)*". Students affected by hearing impairments reported two-times more often symptoms of depression, thoughts about suicide and adverse self-assessed general and mental health. Although this study falls short in validating an intimate relationship between tinnitus and suicide, it does support the notion that hearing impairments and mental health are interrelated pathologies.

Seo et al. (Seo et al., 2016) conducted one of the first large-scale surveys to validate a relationship between suicidal behavior and tinnitus (suicidal thoughts as well as unsuccessful suicide attempts). The authors examined data from 17,446 South Koreans in the Korean National Health and Nutrition Examination Survey (KNHANES). The presence of tinnitus was evaluated by the question: "*Have you ever heard a noise (humming, hissing, ringing, humming, humming, machine noise) in your ear in the past year? (yes/no)*". If answered with 'yes', the authors graded tinnitus severity by the question: "*How severe is this noise in your daily life? (not annoying/ annoying; irritating; severely annoying and causes sleep problems)*". Finally, suicidal thoughts were judged by the question: "*In the last 12 months, did you think about committing suicide? (yes/no)*". If a person confirmed suicidal thoughts, a follow-up question asked for actual suicide attempts. Interestingly, 20.9% of tinnitus patients reported of suicidal thoughts, compared to 12.2% in the healthy cohort and 1.2% of tinnitus patients admitted to have undertaken suicide attempts compared with 0.6% in the healthy cohort. Thus, this study gave first concrete evidence for a relation between tinnitus suicidal thoughts but failed, due to its design, to validate a relation between tinnitus and suicide.

Using data from the same survey, the fourth and fifth KNHANES conducted from 2008 to 2012, Han et al. (K.-M. Han et al., 2018) searched for the presence and severity of tinnitus, depressive mood, suicidal ideation, perceived usual stress level, and socioeconomic and health-related variables in 28,930 adults (aged ≥19 years). As shown in the study by Seo et al. (Seo et al., 2016), tinnitus and its severity associated significantly with the presence of depressive mood and suicidal ideation. Furthermore, the study revealed that tinnitus, depressive mood and suicidal ideation share common socioeconomic and health-related risk factors.

One study was conducted by the National Health Service in the United Kingdom (Aazh and B. C. J. Moore, 2018) in audiology outpatients with tinnitus and hyperacusis to assess the prevalence of and factors related to suicidal and self-harm ideations. 150 out of 402 patients answered the Patient Health Questionnaire, item 9 (PHQ-9), and of these, 13% indicated that they had suicidal or self-harm ideations in the past 2 weeks. Statistically significance was found for correlations between suicidal and self-harm ideations and tinnitus handicap, hyperacusis handicap, insomnia, and VAS scores. Interestingly, suicidal and self-harm ideations decreased with increasing age. A mathematical regression model revealed that abnormal depression scores increase the chance for suicidal and self-harm ideations by factor 6.2. It was concluded that audiologists should be aware of these comorbidities and eventually offer help.

A different approach was used by Martz et al. (Martz et al., 2018). In a large study on 769,934 U.S. veterans seeking medical aid between January 2002 and December 2011, tinnitus was diagnosed in 15% (n =116,358). Of these veterans diagnosed with tinnitus, 21% revealed symptoms of depression, 8% anxiety and 17% a combination of both. Hearing loss was co-occurring in 41.9%. The most surprising finding was that suicide rates among veterans with tinnitus was lower than veterans without tinnitus. Also, the presence of other mental-health comorbidities did not increase the risk of suicide.

Case reports

We identified two publications describing individual cases of tinnitus patients and suicide and categorized them as quasi case reports. One of the first analyses on this issue was conducted by Lewis et al. in 1994 (Lewis et al., 1994). The authors evaluated a 20-idem tinnitus suicide questionnaire obtained from audiological clinics worldwide. 28 cases of suicide were identified from individuals with known tinnitus complaints. The authors pointed out that the onset of tinnitus represents a significant event in life and determined certain risk factors that increase the risk for suicide amongst tinnitus patients, which are male gender, low social economic status, social isolation, bereavement and depression. The study remained descriptive, however, and thus did not allow clear-cut conclusions.

Another report (Frankenburg and Hegarty, 1994) was published on two patients suffering from tinnitus and with documented suicide attempts. The patients had histories of significant psychiatric comorbidities including depression and paranoid disorder. It was concluded that a relation between tinnitus, hallucination, suicidal attempts and depression is possible. But a robust conclusion cannot be made due to the descriptive nature of the study and the low number of cases.

Review articles

In 2001 a literature review on tinnitus and suicide released 1966-2001(Jacobson and McCaslin, 2001) was published. Out of twelve articles identified from their literature search, eight articles were excluded. The sample size in all remaining four articles was small. Interestingly, two articles discussed in this review did not appear according to our more stringent criteria. The authors claim that a predictive relationship between tinnitus and suicide cannot be concluded. Instead, the authors suggest that not tinnitus *per se* provokes suicidal ideation, but a combination of psychiatric comorbidities increases the suffering from tinnitus and trigger the fatal decision.

A literature review on suicide in deaf populations was conducted (O. Turner et al., 2007) and 13 related reports were identified. Little evidence was found to suggest that risk factors for suicide in deaf people differ from those in the general population and just as seen for tinnitus, a higher level of depression and perceived risk for suicide was found among compared to control groups. Interestingly, Turner et al. discuss in detail a number of articles on tinnitus and suicide without offering a conclusive answer on a possible correlation.

Pridmore et al. (Pridmore et al., 2012) investigated a possible link between suicide and tinnitus by searching in newspapers and the internet for 'stories' over the past decade. They reported four cases in which tinnitus appeared to precede suicide. The researchers have noticed that, the data presented in their article are anecdotal and cannot provide reliable arguments for or against a causal relationship between tinnitus and suicide. Nevertheless, it was suggested that health professionals should be attentive to those who are significantly concerned about their tinnitus and refer them to mental health providers.

5.5 SOUND PERCEPTION OF TINNITUS PATIENTS

All sounds were labeled differently according to their frequency. In the first task 50% of the tinnitus patients top-rated "beeping" as the adjective to best describe their tinnitus. All pure tones (0.125, 1, 8, 16 kHz) were most of the percentage listed as a tone (30-47%), all other given adjectives describe sounds like roaring, humming, whining, hissing, wailing, rumbling; accept the 0.125 kHz tone, which was labeled in 11% as honking tone. The AM tones were described as follow: 0.125 kHz: 30% tooting, 20% roaring, 1kHz: 41% beeping, 27% whining, 8 kHz: 24%whining, 24% cricket like, 16 kHz: 33% beeping, 13% cricket like. The 1/3-octave-band noise centered at different frequencies were most of the percentage perceived as roaring and humming (20%), whining (32%), hissing (30%), swooshing and hissing (36%). If the given noise was amplitude modulated the adjectives change to cricket-like (59%), hissing (37%), humming (24%). Water-like sounds were identified for broad-band pink noise (30%), while the most given description for that noise was roaring (35%).

The highest intraclass correlation was found for pink noise (ICC: 0.578), meaning that for pink noise, the participants rated the descriptiveness of the given adjectives in the most consistent way among the current set of sounds. The lowest intraclass correlation was found for the 1-kHz AM noise (ICC: 0.107).

For all other played sounds (16, see in the "Subjects and methods") no correlation was observed. Also, in the usage of the sound describing adjectives no correlation was found (Krippendorff's alpha >0.5).

6 DISCUSSION

Tinnitus describes the sensation of a tone, whistle, beep or other noise in the absence of a physical sound. It may be the symptom of a cochleopathy but exact anatomical correlates have not been found and disease etiologies are still under debate. Tinnitus may be the consequence of noise exposure, trauma, psychological stress situation, age, genetic predisposition or a combination of all. As a consequence, current treatment approaches are largely symptomatic and thus do not offer a cure. One rare exception to this notion may be the electric stimulation via a cochlear implant, which has proven to be well-tolerated and effective in restoring hearing in deaf people (Elgandy et al., 2018). Despite some tests with apparent positive outcome in tinnitus patients (Elgandy et al., 2018), the U.S. Food and Drug Administration did not yet approve this as a tinnitus therapy. Thus, more research is needed to explore this option. Although tinnitus itself is not lethal, it is a condition best described as debilitating and may induce depression and may promote suicidal thoughts and actions. It may equally be a comorbidity of another psychiatric condition. In brief, since tinnitus is difficult to quantify, if measurable at all, any clinical observation that may uncover etiologic relationships are of great importance to better understand the disease, the suffering and to implement a therapeutic approach.

Here, medical records were retrospectively analyzed to identify risk factors leading to tinnitus, e.g. regular listening to music. Furthermore, children have been identified as equally affected. Altogether, this shall sensitize medical personnel, nurses and doctors, but also family members for the disease, the individual suffering and adverse consequences, e.g. suicidal acts. Finally, novel experimental attempts were undertaken to grade or actually visualize the degree of suffering. Two mutually independent approaches were followed. First, tinnitus was compared to the individual affective processing, i.e. giving tinnitus a score or subjective ratings. Second, tinnitus was quantified using surrogate parameters such as unconscious responses of the autonomous nerve system, i.e. pupillometry.

6.1 MUSIC INDUCED HEARING DISORDERS

The present study investigated 104 consecutive tinnitus patients who had experienced loud music exposure and consequently developed a hearing disorder. The results reveal that music can cause an acute trauma with subsequent various degrees of hearing impairments, above all tinnitus. Severity of tinnitus (THI) and its subjective ratings correlated strongly with each other but not with hearing loss as recorded by tone-audiograms. Our data support the results of previous studies in both mice and guinea pigs showing that there is a loss of roughly 50% of the synapses on all hair cells throughout different cochlear regions after a noise exposure (Kujawa and Liberman, 2009; Lin et al., 2011). This dramatic CS can occur in the absence of hair cell loss. With progressing CS, the affected neuron is functionally disconnected from the hair cell and thus carries no auditory information to the central nervous system. It is important to conclude that every sound exposure above certain levels poses a risk to develop CS, which due to the lack of clinical correlates was coined 'hidden' hearing loss (HHL) (Kujawa and Liberman, 2009; Schaette and McAlpine, 2011). Here, we confirm that tinnitus and hearing loss can emerge independently but due to the lack of objective audiometry methods and the restricted observation period it is invalid to conclude correlations. Nevertheless, support for tinnitus as an early symptom of CS comes from another study (Schaette and McAlpine, 2011), where a reduced amplitude of ABR wave I was found in tinnitus patients with normal hearing thresholds. There is evidence that noise exposure in the past is associated with difficulties in speech discrimination and temporal processing, even in the absence of any audiometric loss (Plack et al., 2014). This is also of importance for the well-described abuse of headphones, which is apparently underrepresented in our study. We assume that we undervalue the real number of affected because headphones are used primarily by the very young while symptoms become evident relatively late, sometimes without experiencing a singular trauma. Extensive information campaigns within groups of risk shall significantly decrease the incidence. This can be concluded from the fact that professional musicians were less often affected than the visitors of their concerts. Proper risk recognition leads to the use of ear protection and down tuning of on-stage monitors while visitors are still unprotected in the crowd. Taken together, the present study shows a high occurrence of tinnitus experienced after an acoustic overstimulation by loud music. Current concepts show that tinnitus (or other noise-induced impairments) may represent a warning sign for beginning CS. The problem of MIHD is widespread in the general population but under-perceived since impairments accumulate over time also from nonpathogenic noise exposures. Concerted information campaigns using social networks are needed to reach the adolescents at risk. Only a better understanding of MIHD and public awareness will allow music enjoyment without exposure to noise.

6.2 TINNITUS IN CHILDREN

The aim of the study was to compile clinical data that characterize tinnitus in pediatric patients. The retrospective design of this study allowed a quick survey over a period of five years. At the same time, this is its biggest limitation as all information is to medical records and follow-up examinations are not possible.

The most troublesome result of this study is the confirmation of pediatric tinnitus as a largely ignored symptom. The time between the first appearance of symptoms and a presentation in our clinic was slightly above 12 months. It seems that children with the first symptoms of tinnitus are diagnosed and treated for too long in local services and referred to a special clinic as last resort. The reason for this unexpected pattern may be that children do not generally report tinnitus spontaneously and their complaints may not be taken seriously enough (Mills et al., 1986). It has also been suggested that children consider the presence of the ear noises as normal. This is especially true if they have had it for a long time, or if they are distracted from their environment, for example, when playing with their favorite toys or enjoy other activities that makes them forget it (Aksoy et al., 2007).

Our data disclose that tinnitus in children is not necessarily connected to hearing loss and cannot always be related to an initiating trigger. Most children in our study had normal hearing abilities while inversely, the prevalence of tinnitus is up to 46% (Juul et al., 2011)in children with normal hearing threshold and 62% (Graham, 1981) in children with hearing loss. Also, in our patients group a history of middle ear pathology was reported in only 12 %, which seems not to be a significant factor in the genesis of tinnitus in children. This result is in line with previous studies where no statistical differences between children with or without middle ear pathology was found (Mills and Cherry, 1984; Savastano, 2002). In contrast, we identified jaw misalignments and malocclusions treated by orthodontics as the most common trigger. The relationship between the two is still only partially understood (Rubinstein, 1992), nevertheless, the prevalence of tinnitus in patients with jaw misalignments and malocclusions ranges up to 76% (Tuz et al., 2003), which is a much higher rate than that of the general population.

Of the included children, 14% reported a noise exposure-initiated tinnitus. Leisure time noise exposures earlier considered playing only a minor role as a health hazard is more and more recognized as a major risk factor. Adolescents and teenagers often expose themselves to loud music and excessive noise levels during social and music events: noise levels between 104 and 112 dB (A) can be measured in nightclubs and discos (Gilles et al., 2013). A recent study on students at British universities showed that 88% of students experienced tinnitus after leaving a nightclub and 66% suffered from music-induced hearing disorder in the following morning. It was also reported that the use of hearing protection, and knowledge about the risks of loud music were negligible (Johnson et al., 2014). There is now evidence that prior noise exposures can exacerbate and accelerate age-related hearing loss and can cause irreversible neural damages in the absence of elevated hearing thresholds (Kujawa and Liberman, 2009; 2006).

6.3 AFFECTIVE PROCESSING IN TINNITUS PATIENTS

In this study we show, that subjective ratings by tinnitus patients differed from normative ratings especially in the positive sound category, where the valence of sounds was rated significantly below those reported in the IADS reference document. This finding is in line with the results reported by Fournier et al. (2014), who compared responses between a tinnitus group and a non-tinnitus control group and found that tinnitus sufferers rated positive emotion-carrying sounds and images as less positive compared to the control group, whereas ratings of negative and neutral stimuli did not differ between the groups. Our results are also in full accordance with the study by Carpenter-Thompson et al. (2015) who found that the response of the limbic system differed between tinnitus and control subjects for the positive sounds when analyzing sound-evoked brain activity with fMRI (Carpenter-Thompson et al., 2015). We were able to support this finding by pupillometry, which shows the same response attenuation for positive sounds.

The diminished valence ratings of positive sounds are similar to those seen in subjects with depressive symptoms. While viewing images of positive and negative content, depressive patients have repeatedly been shown to differ from control groups only in the positive and not in the negative or neutral categories (Berenbaum and Oltmanns, 1992; Dunn et al., 2004; Sloan et al., 1997; 2001). These findings have been explained to underpin the so-called positive attenuation hypothesis of depression, which suggests that depression is best characterized by a lack of positive affect instead of excessive negative affect (Bylsma et al., 2008). Tinnitus and depression also often co-occur (Baguley et al., 2013; H.-J. Kim et al., 2015; Lockwood et al., 2002; McKenna et al., 2014; Nondahl et al., 2011), and it is possible that the current results reflect the comorbid depression rather than any mechanism that would be specific only for tinnitus. Unfortunately, we did not collect data regarding the depressive symptoms of the subjects, but the findings that the dampening of positive affect may be preceded by depressive symptoms could mean that the relationship between depression questionnaire scores and valence ratings might not be so straightforward. Anyhow, future studies in tinnitus involving the use of affective stimuli could benefit from controlling for depression symptoms.

We were not able to show an effect of tVNS on the subjective ratings or on the pupillometric results. Previously, invasive VNS has been shown to induce a pupil dilation in a study without auditory or other stimuli presented during measurement (Desbeaumes Jodoin et al., 2015). An explanation for finding no effect of tVNS is that tVNS and pupillometry are presented by different parts of the autonomic nervous system, and therefore no effect could be found. The auricular branch of the vagus nerve, targeted in tVNS, is part of the parasympathetic system (Badran et al., 2018a; 2018b; Kraus et al., 2007), while the pupil size is controlled by the sympathetic and parasympathetic systems (Eckstein et al., 2017; Laeng et al., 2012). It has been shown that the pupil dilation in response to affective sounds is mostly reflected by the sympathetic nervous system activity (Bradley et al., 2008). That's why the possible effects of tVNS may not be directly displayed in the pupil response. Other measures of autonomic system activity with a more direct target to the parasympathetic system, such as heart rate variability might be better suited for monitoring the acute effects of tVNS (Clancy et al., 2014; Ylikoski et al., 2017).

This is the first study investigating the pupil responses to affective sounds in tinnitus patients. Pupillometry is a relatively inexpensive and easy approach to be administered in the evaluation methods of tinnitus patients. The study demonstrates that pupillometry can be used as a feasible option for studying autonomic activation in tinnitus patients.

6.4 TINNITUS AND SUICIDE

Among developed countries, Finland has a relatively high suicide rate. This is in contrast to the overall positive perception of living condition. In 2013, the average mortality rate from suicide in Finland was 16.4 individuals per 100 000 populations as compared to 12.8 in countries organized in the Organization for Economic Co-operation and Development (OECD). Suicidal thoughts and initial attempts may precede actual suicide completion (Jacobson and McCaslin, 2001). The most prominent risk factor therefore is depression. The link between tinnitus and emotional disorder has been investigated in several studies (Andersson et al., 2009; Malouff et al., 2011). Tinnitus can vary in its phenomenological characteristics and in the amount of the related distress. It can cause severe distress on individuals and has been shown to be correlated with sleeping disorders, depression and anxiety. It may affect the individual's concentration and ability for attentional focusing and working memory and tinnitus can act as an additional stressor of suicide completion (Lewis et al., 1994). Thus, to decrease rates of completed suicide, it is very important to identify associated warning signs and risk factors.

In this review we wanted to investigate if and how tinnitus can trigger suicidal thoughts, suicide attempts and completed suicides. Obviously, all attempts to solve this problem are hindered by the fact that suicidal thoughts and behaviors have multiple causes. We identified ten articles, five of which describe prevalence studies, two discuss case reports, and three reviewed the topic.

In our opinion, the very few prevalence studies (Aazh and B. C. J. Moore, 2018; Lee et al., 2018; Martz et al., 2018; Seo et al., 2016; Vogel et al., 2014) are of paramount importance, even though they suffer from a variety of limitations. One limitation is that tinnitus is rarely an isolated event. It may occur in addition to or in combination with other pathologies or trigger the development of psychiatric comorbidities such as anxiety and depression. It has been reported previously that post-traumatic stress disorder and depression alone trigger suicidal behavior (Martz et al., 2018). Another limitation is due to the fact that current questionnaires can only deal with suicidal thoughts or unsuccessful suicide attempts. In fact, four out of five prevalence studies, which relied on self-reporting questionnaires, have shown that tinnitus causes suicidal thoughts to varied degrees (Aazh and B. C. J. Moore, 2018; K.-M. Han et al., 2018; Seo et al., 2016; Vogel et al., 2014). The other study, based on retrospective ICD-9-CM/ICD-10 analysis, showed that suicide rate among tinnitus patients was lower than in controls (Martz et al., 2018), but this study is addresses only successful suicides and not attempts or ideations. Therefore, all self-reported questionnaires may result in too negative answers and thus over-interpret a possible context.

Tinnitus and depression also often co-occur (Baguley et al., 2013; H.-J. Kim et al., 2015; Lockwood et al., 2002; McKenna et al., 2014; Nondahl et al., 2011). Patients suffering from tinnitus show attenuation of positive valence in ratings of affective sounds, which is very similar to responses seen in patients suffering from depression. In addition, blunted stress hormone levels, such as cortisol, have been reported in patients with tinnitus and depression (Hébert and Lupien, 2007). Decreased cortisol responses indicate the presence of severe forms of endogenous depression and are considered to be a negative predictor of subjective stress and tinnitus intensity (Hébert and Lupien, 2009).

In order to better understand the relationship between stress reactions in tinnitus and / or depression, further studies are needed that specifically address the sequence of events and their consequences.

To express it differently: is a blunted stress response a prerequisite for the development of tinnitus and/or depression or is the presence of tinnitus and/or depression the reason for the diminished response. Also, if tinnitus and possibly psychiatric comorbidities alter hormonal stress responses similarly, is the effect additive and thus suicide more likely if tinnitus is accompanied by comorbidities or is only the degree of stress response attenuation relevant to which all signaling cascades converge individually?

6.5 SOUND PERCEPTION OF TINNITUS PATIENTS

Tinnitus patients describe given simple sounds (pure tones and narrow-band noise) very widespread. No correlation could be found in the labeling of the given external sounds, accept broad-band noise. Our results are in line with a previous study by Wahlström & Axelsson (1995), where also no correlation could be found between the person's labeling of their own tinnitus sound and the earlier given subjects. In their study low-level, but audible pure tones of different frequencies were presented to tinnitus patients and they were then asked to describe, what they have heard. The 4-kHz tone was only listed in 34% of cases as a tone, in 26% as a hissing sound, in 18% as a roaring sound, and in the remaining 22% as whistling, squeaking, etc. An 8-kHz tone was described as rushing in 48%, in 16% as beeping, in 12% as ringing and the remainder as whistling, a cricket sound, a dentist drill, etc. Further, we found also another interesting aspect. The subjects in our study seemed to agree more on the top-rated adjectives than in the poster by Wahlström & Axelsson (1995). For example, beeping was the top-rated adjective in 50% of the participants in our study, whereas in the poster only 16% described the sound as beeping.

It seems that the characterization of external sounds, and also internal percepts such as tinnitus, is not easy especially for people with tinnitus who have a cochlear damage (cochlear synaptopathy, inner or outer hair cell loss), that can produce distortion of sound.

The same difficulties to describe pure tones are reported by hearing impaired subjects. It has been suspected that a pure tone might be perceived as noise-like when the tone produces maximum arousal fall in the dead region of the cochlea (Florentine and Houtsma, 1983; Huss and B. C. J. Moore, 2005).

Psychoacoustic models of tinnitus have mostly been dealt with patient reports of tinnitus pitch and loudness (Penner, 1986; 1983; Penner and Saran, 1994). Nowadays there is a need to close the gaps between perception, cognition and contextual effects (Searchfield, 2014). Auditory perception should be seen as an interplay with the acoustic and social environment and the individual's perception of self (Searchfield, 2014). The individual perception is influenced by hearing impairment, physical (Nondahl et al., 2011) and mental health (Brunnberg et al., 2008; J.-S. Kim, 2018), memories and past experience (Zenner et al., 2006). Environmental aspects include for instance day time, social venue, work, home and activity and social factors like relationship, values, customs or beliefs (Searchfield, 2014).

That indicates, that the subjective descriptions of tinnitus sound, or basically any sound, should be interpreted with great care. Since people seem to not agree intuitively about the adjectives that they would use for very controlled and simple sounds, these descriptions should not be used as grouping variables in studies.

Taken together, tinnitus is difficult to diagnose and even more difficult to quantify. Its description relies entirely on the very subjective description of the affected. This work shed new light on actual insults of tinnitus and revealed the surprising finding that listening to music already represents an insult and it puts special focus on patients that have been largely neglected, i.e. children. More interesting, however, were attempts to add quantitative measures to the clinical diagnostics. Novel technologies and innovative new approaches were tested that may, in the future, offer a sensitive means to visualize the suffering in order to acknowledge the disease and to optimize and follow up treatment attempts. If successful, such approach would revolutionize clinical work and hopefully decrease suffering – making tinnitus a manageable and less debilitating condition.

7 CONCLUSIONS

Study I
Music-induced acute acoustic trauma is not inevitably linked to hearing dysfunction as validated by conventional pure tone audiometry. Our results point out "silent hearing loss" as the underlying pathology, that may have afferent nerve terminal damage rather than hair cell loss as the structural correlate.

Study II
Tinnitus in the childhood deserves better recognition and a detailed characterization of symptoms and triggers is mandatory to sensitize medical personnel and care takers for the suffering since ignoring the impairment can have severe developmental consequences. We propose that any type of pediatric tinnitus should be seen by specialists to initiate proper diagnostics and treatments at the earliest possible time-point to avoid adverse consequences.

Study III
Our results highlight the close link between tinnitus and depression. The current study demonstrates that pupillometry can be considered a viable option for studying autonomic activation in tinnitus subjects. In addition to affective processing, pupillometry—by itself or combined with eye gaze information—can also be utilized in experiments designed to probe the working memory, attention, or cognitive control, which are also important lines of investigation in tinnitus.

Study IV
From the above-mentioned literature, we cannot univocally conclude if tinnitus and suicide are interrelated entities. There is good evidence, that severe forms of depression and tinnitus show altered stress responses such as lowered cortisol levels. Further studies are needed to validate this notion.

Study V
Subjective tinnitus descriptions should be interpreted with great caution. Tinnitus patients do not agree intuitively on an adjective for best description even under very controlled conditions using simple sounds as applied in this trial. This generally invalidates the use of adjectives as cluster variables for the description of tinnitus sounds.

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