Psychophysiological Treatments and Neural Correlates of Chronic Tinnitus

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Manuel Czornik

aus Stuttgart

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Dekan:	Prof. Dr. Thilo Stehle
1. Berichterstatter:	Prof. Dr. Martin Hautzinger
2. Berichterstatter:	Prof. Dr. Dr. hc. mult. Niels Birbaumer
3. Berichterstatter:	Prof. Dr. Michael Schönenberg

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List of Contents

List of Figures

List of Abbreviations

ADHD	Attention deficit hyperactivity disorder
Ag/AgCl	Silver/silver chloride
AMV	Absolute maximum value
AUC	Area under the curve
BA	Brodmann area
BDI	Beck Depression Inventory
CBT	Cognitive behavioural therapy
CI	Cochlear implant
CNS	Central nervous system
DBS	Deep brain stimulation
DCN	Dorsal cochlear nucleus
dlPFC	Dorsolateral prefrontal cortex
EEG	Electroencephalography
EMA	European Medicines Agency
ENT	Eye-Nose-Throat
FDA	Food and Drug Administration
fMRI	Functional magnetic resonance imaging
fNIRS	Functional near infrared spectroscopy
FPC	Frontopolar cortex
GABA	Gamma-aminobutric acid
HPA	Hypothalamus-pituitary-adrenal
IHC	Inner hair cell
LC	Locus ceuruleus
LI	Left intensity

MDD	Major depressive disorder
MEG	Magnetencephalography
MSI	Magnetic source imaging
MTG	Middle temporal gyrus
OFC	Orbitofrontal cortex
OHC	Outer hair cell
PET	Positron-emission tomography
PSQI	Pittsburgh Sleep Quality Index
rCBF	Regional cerebral blood flow
RCT	Randomized controlled trial
RI	Right intensity
rTMS	Repetitive transcranial magnetic stimulation
sgACC	Subgenual anterior cingulate cortex
sLORETA	Standardized low resolution brain electromagnetic tomography
SNS	Sympathetic nervous system
SOAEs	Spontaneous otoacoustic emissions
STAI-T	State and Trait Anxiety Inventory - Trait
tDCS	Transcranial direct current stimulation
TD	Tinnitus duration
THI	Tinnitus Handicap Inventory
TMNMT	Tailor-made notched music training
TRN	Thalamic reticular nucelus
TRT	Tinnitus retraining therapy
QEEG	Quantitative electroencephalography

Abstract (English)

Subjective chronic tinnitus is a continuous or intermittent auditory percept without an external source, which is often accompanied by hearing deficits. As indicated, it is characterized by an absence of a corresponding acoustic source, not heard by anyone else, and may lead to various psychological problems including sleep disorder, depression, and anxiety. This dissertation aims to identify therapy and management options as well as to reveal some neural correlates of tinnitus severity and accompanying mood and anxiety disorders. Thus, the efficacy of various treatment approaches including psychotherapy, sound therapy, pharmacological therapy, and both non-invasive and invasive brain stimulation is evaluated. Albeit there are some therapies that surpass placebo effects, such as cognitive behavioral therapy (CBT) or neuromodulation techniques, they mainly influence secondary symptoms but not the tinnitus tone itself, and the effects usually last for a limited time only. To investigate the differential neuronal profile of patients with severe and less severe chronic tinnitus 34 tinnitus patients were assigned to two groups and their EEG resting state activity was compared. Using a source analysis approach a significant and substantial frontal increase in theta wave activity was found in the group with severe tinnitus. The correlated severity of depression and anxiety did not correlate with the electrophysiological metrics. These results support a tinnitus-related global network change in which prefrontal areas are part of a network which exerts a top-down influence on the auditory cortices. The magnitude of this influence may be linked to the subjective strength of the tinnitus distress. Therapies should focus on both reducing the hyperactivity in the auditory cortex and reducing the top-down influence of the tinnitus-related global network on the auditory cortical and subcortical systems.

Abstract (German)

Subjektiver chronischer Tinnitus ist eine dauerhaft oder mit Unterbrechungen auftretende auditorische Wahrnehmung, welche oft mit Schwerhörigkeit einhergeht. Sie ist charakterisiert durch die Abwesenheit einer Schallquelle (wird von niemandem sonst gehört) und kann zu vielfältigen psychologischen Problemen wie Schlafschwierigkeiten, Depressionen und Ängsten führen. Diese Dissertation hat das Ziel, Behandlungsmöglichkeiten darzulegen und die neuronalen Korrelate des chronischen Tinnitus und begleitender Affekt- und Angststörungen zu dokumentieren. Daher wird die Wirksamkeit verschiedener Behandlungsansätze einschließlich Psychotherapie, Soundtherapie, pharmakologischer Therapie sowie nicht-invasiver und invasiver Hirnstimulation bewertet. Obwohl es einige Behandlungen wie die kognitive Verhaltenstherapie oder Neuromodulationstechniken gibt, die Placebo-Effekte übertreffen, beeinflussen sie hauptsächlich sekundäre Beschwerden aber nicht den Tinnitus-Ton selbst. Des Weiteren halten die Effekte der Therapien oft nur eine begrenzte Zeit an. Um die unterschiedlichen neuronalen Muster von Patienten mit schwerem und weniger schwerem chronischem Tinnitus zu untersuchen, wurden 34 Tinnitus-Patienten einer dieser beiden Gruppen zugeordnet und die EEG-Ruhezustandsaktivität der beiden Gruppen verglichen. Unter Verwendung einer EEG-Source-Analyse wurde in der Gruppe mit schwerem Tinnitus ein signifikanter Anstieg der Theta-Aktivität in frontalen Hirnregionen festgestellt. Der Schweregrad von Depressionen und Ängsten hatte keinen Einfluss auf die elektrophysiologische Metrik. Diese Ergebnisse unterstützen die Annahme Tinnitus-bedingter Veränderungen im Gehirn, bei denen präfrontale Bereiche Teil eines Netzwerks sind, welches einen Top-down-Einfluss auf die auditorischen Kortizes ausübt. Die Größe dieses Einflusses hängt mit der subjektiven Stärke der Tinnitus-Belastung zusammen. In Bezug auf die Therapie von Tinnitus wird impliziert, dass

sich Behandlungen sowohl auf die Verringerung der Überaktivität im auditorischen Kortex als auch auf die Verringerung des Top-down-Einflusses des Tinnitus-Netzwerks auf den temporalen Kortex fokussieren sollten.

List of Publications

Accepted Publications:

Malekshahi, A., Malekshahi, R., Czornik, M., Dax, J., Wolpert, S., Bauer, H., ... & Birbaumer, N. (2020). Real-Time Monitoring and Regulating Auditory Cortex Alpha Activity in Patients with Chronic Tinnitus. *Journal of Neural Engineering*, *17*, 016032. doi.org/10.1088/1741-2552/ab57d5

For details, see appendix.

Objective

This dissertation presents an overview of current psychophysiological approaches for tinnitus treatment and an evaluation of their efficacy if outweighing placebo (Dobie, 1999; 2004). Thus, it shall be evaluated which treatment approach is the “gold standard”, which is promising and where more research is needed until implemented in clinical settings. Therefore, we focus on controlled studies and meta-analyses.

Furthermore, the neural correlates of tinnitus and accompanying mood disorders such as depression and anxiety shall be analyzed. A sample of chronic tinnitus patients were assigned into two groups of patients: those with severe and those with non-severe tinnitus. The EEG resting state was compared between the two groups using spectral analyses and source localization by means of standardized low-resolution brain electromagnetic tomography (sLORETA; Pascual-Marqui, Esslen, Kochi, & Lehmann, 2002). In a second assignment, we compared tinnitus patients with signs of mood or anxiety disorder to tinnitus patients without these symptoms. It was suggested that better understanding of the brain activation in tinnitus both with and without depression, anxiety, and sleep problems will help to disentangle the confusion about neural alterations in those tinnitus patients with severely reduced quality of life and will allow to identify the most relevant brain regions and brainwaves in part responsible for tinnitus and/or for mood disorder and anxiety.

In a third step, it shall be investigated how neural correlates of tinnitus and accompanying mood disorders are related to the efficacy of different treatments for tinnitus and which implications can therefrom be derived to achieve long-lasting therapeutic effects. We are aware of the fact that the data collected in this

dissertation is just a first step towards a more complete psychophysiological model of chronic tinnitus.

Chapter One: Psychophysiological Treatments of Chronic Tinnitus

Introduction

Subjective chronic tinnitus defines a prevalent symptom characterized by an auditory sensation in the absence of a corresponding acoustic stimulus which can be continuous or intermittent and has to last for more than 3 or 6 months, depending on the classification system used (Hesse, 2008). Patients often experience more than one sound simultaneously, and in many cases, hearing deficits also occur (Axelsson & Ringdahl, 1989; Nicolas-Puel et al., 2006). The term originates from the Latin word “tinnire”, which means to ring or to tinkle. Since it is not caused by a recordable sound in or outside of the body, per definition and in contrast to objective chronic tinnitus, subjective tinnitus cannot be perceived from any individual besides the tinnitus sufferer himself (Chan, 2009). Thus, in subjective tinnitus an altered sensation represents the problem, whereas in the very rare objective tinnitus an abnormal sound from the body, mainly from the inner ear, causes an auditory sensation (Lanting, de Kleine, & van Dijk, 2009).

In contrast to acute tinnitus, the time limited tinnitus which nearly everyone has experienced at some moments in their life, the prevalence of subjective chronic tinnitus is estimated to effect 10–15% of the general population (Axelsson & Ringdahl, 1989; Heller, 2003; Shargorodsky, Curhan, & Farwell, 2010) and seems to increase with age as epidemiological studies suggest (Ahmad & Seidman, 2004; Salomon, 1989). Sometimes tinnitus can be a rhythmical or a pulsatile sound. If the pulsatile tinnitus is synchronous with the heartbeat, a vascular origin is probable; if it is asynchronous, then a myoclonus of palatal or middle-ear muscles is likely (Bhimrao, Masterson, & Baguley, 2012). Individuals suffering from tinnitus often localize their tone to one or both ears, but some also perceive it centrally within the

head. With regard to the prevalence, about half of all patients perceive the sound in both ears or centrally within the head, whereas the other half perceive it on one side only (Coles, 1984). Among the latter, tinnitus is more frequently experienced on the left than the right side. The reason for this preponderance, however, is unclear and cannot be explained by an asymmetry of hearing loss (Meikle & Griest, 1992).

The degree to which tinnitus patients suffer is not consistent and varies depending on the involvement of accompanying psychological problems including depression and anxiety. Around 3–5% of the general population perceive their tinnitus as being extremely disturbing since their lives are seriously affected not only by pain, discomfort, and sleep problems, but also mood and anxiety disorders to such a magnitude, that it makes it difficult for the affected persons to perform everyday activities (Bhatt, Bhattacharyya, & Lin, 2017; Davis & El Refaie, 2000; Stobik, Weber, Munte, Walter, & Frommer, 2005).

Pathophysiology of Tinnitus

Since the sensation of hearing, and hence tinnitus, are usually associated with the ear, it would be obvious at first glance to assume pathophysiological alterations in the ears of tinnitus sufferers. However, such changes can only be detected in some tinnitus sufferers. Thus, it is unclear which role the inner ear and particularly the cochlea play in tinnitus development. Some researchers emphasize the role of the cochlea in tinnitus emergence and suggest that the missing evidence of a cochlear deficit in some tinnitus patients results from the lack of sufficiently sophisticated diagnostic techniques (Lindblad, Hagerman, & Rosenhall, 2011). These concepts are in accordance with the so-called discordance model, the edge theory (also known as contrast theory), and theories emphasizing the role of spontaneous otoacoustic emissions (SOAEs). According to the former, tinnitus is provoked by a “discordance”

in the organ of Corti of the cochlea between damaged outer hair cells (OHCs) and not-damaged intact inner hair cells (IHCs) due to a higher sensitivity of OHCs against intensive noises and ototoxic substances (Jastreboff & Hazell, 1993). The edge theory supposes that tinnitus is caused by increased spontaneous activity in afferent fibers on the basal side of a lesioned organ of Corti in the so-called edge area. This area represents a transition from relatively normal functioning OHCs on the organ of Corti's apical (or low frequency) side of a lesion to missing or pathological OHCs towards the basal side with poor functionality (Kiang, Moxon, & Levine, 1970).

SOAEs are acoustic signals generated by the electromotile activity of the OHCs without acoustic stimulation and spread into the external auditory canal (Brownell, 1990; Kemp, 1978). Albeit normally inaudible, SOAEs can become audible and be perceived as tinnitus. These audible SOAEs occur more frequently in the higher frequency range (Mathis, Probst, De Min, & Hauser, 1991). As hearing loss progresses, SOAEs decrease. Thus, according to Probst, Lonsbury-Martin, Martin, and Coats (1987) it is not likely that SOAEs cause tinnitus when a hearing loss surpasses 35 dB. Tinnitus due to SOAEs is common in individuals with normal hearing or middle ear disorders and normally associated with non-severe symptomatology (Kemp, 1981). Another argument against SOAEs as far-reaching explanation for tinnitus is the evidence that aspirin intake abolishes SOAEs without having a positive effect on tinnitus (Penner & Burns, 1987).

The cross-talk theory proposes that some forms of tinnitus are associated with abnormal phase-locking of unloadings in groups of auditory nerve fibers. Certain cranial nerves are covered by myelin at the root entry zone, where they are sensitive to compression. The decay of the myelin insulation of the nerve fibers constitutes ephaptic coupling between them. This also applies to the cochlear-vestibular nerve (also known as auditory vestibular nerve or cranial nerve VIII). It is covered by myelin

for the most part and is susceptible to compression from veins or tumors impinging upon it (e.g., vestibular schwannoma). Such compression and subsequent ephaptic coupling are assumed to lead to phase-locking of spontaneous activity of clusters of neurons, which in the absence of external sounds generate a neural pattern that resembles that elicited by sound (Møller, 1984).

According to neuroplasticity theory, damage to the cochlea can lead to a reduced afferent input to the central auditory system (Pantev, Okamoto, & Teismann, 2012). In order to compensate for and adapt to this modification, which is highly correlated with hearing loss, the function of several auditory pathway structures alters and in turn may lead to tinnitus. In the topographically organized auditory cortex in regions adjacent to the region that is deprived of input, the representation of sound is augmented as a contrast enhancement phenomenon. This means an increased responsiveness of neurons deprived of thalamocortical input towards frequencies adjacent to the regions that represent the frequencies where hearing is disturbed through lateral connections of the apical dendrites (Bartels, Staal, & Albers, 2007; Eggermont & Roberts, 2004; Weisz, Dohrmann, & Elbert, 2007a; Weisz et al., 2007b).

Based on neuroanatomical findings and analogies with other clinical conditions such as phantom limb pain, Simpson and Davies (2000) suppose that noise damage or other initial lesions induce plastic alterations in central auditory structures which trigger a change in neurotransmission resulting in a change of serotonin (5-HT) receptor configuration. It is suggested that 5-HT activation in sensory neurons may compensate for malfunction of sensory input and processing. It seems likely that tinnitus perception could be related to a dysfunction of 5-HT at one or multiple levels in the central nervous system (CNS) (Liu, Li, Wang, Dong, Han, & Liu, 2003; Simpson & Davies, 2000). Due to the negative consequences of these neural

alterations – the perception of tinnitus – they are referred to as reflecting the “dark side” of cortical plasticity (Pantev et al., 2012).

Furthermore, evidence is accumulating that apart from the initial pathology, tinnitus is a much more complex phenomenon also involving neurocognitive and neuroemotional networks, and cross-modal effects such as abnormal interactions between sensorimotor, somatosensory, and visual-motor systems (Andersson & McKenna, 2006; Cacace, 2003; Møller & Rollins, 2002). It could be shown that attentional and emotional states can be involved in the emergence and maintenance of tinnitus via top-down mechanisms (Shore, Roberts, & Langguth, 2016). In a similar way, altered somatosensory input can have an effect at auditory pathways, which is shown by head injuries or skin stimulation that lead to tinnitus or a modulation of tinnitus intensity (Møller, 1997). This may be a sign of re-routing of tactile information similar to neuropathic pain patients who experience pain from cutaneous stimulation that is normally innocuous. Thus, analogous to phantom pain sensations, tinnitus can be regarded as an auditory phantom percept (Flor et al., 1995; Lockwood et al., 1998). Further similarities between tinnitus and phantom pain include that both are often accompanied by psychological comorbidities such as affective disorders as well as specific abnormalities in the perception of sensory stimuli such as tinnitus patients suffering from hyperacusis (Møller, 2003).

Etiology of Chronic Tinnitus

The causes for tinnitus are unknown and many patients are not able to identify any trigger linked to the tinnitus onset. In some cases, the emergence is linked to otological diseases that can occur along the auditory pathway, such as sudden hearing loss, noise trauma, presbycusis (age-related hearing loss), otosclerosis (a disease with calcification of the bony labyrinth), or Meniere’s disease (a disorder of

the inner ear that is also characterized by vertigo and hearing loss). Further disorders that are associated with tinnitus are infectious diseases, such as meningitis (an acute inflammation of the meninges) or otitis media (a group of inflammatory diseases of the middle ear); neurological diseases, such as vestibular schwannoma (a benign tumor emerging in the vestibulocochlear nerve); and head injury (Baguley, Andersson, McFerran, & McKenna, 2013a; Han, Lee, Kim, Lim, & Shin, 2009; Langguth, Kreuzer, Kleinjung, & De Ridder, 2013; Nondahl et al., 2011). In addition to being a symptom of the aforementioned disorders, tinnitus can also occur as a side effect from the intake of antibiotics, chemotherapy agents, or high doses of aspirin, and after traumatic life events such as bereavement or traffic accidents (Han et al., 2009).

Theories of Tinnitus

The Psychological Model of Tinnitus

In the psychological model of tinnitus by Hallam, Rachman, and Hinchcliffe (1984), it is stressed that, although tinnitus might be caused by abnormal neurophysiological signals at any level of the auditory system, research shows that the degree of disability and suffering does not simply reflect the degree of neural dysfunction (Rachman & Philips, 1980). Thus, derived from the research on headache sufferers, it is supposed that psychological factors play an important role in the manifestation of tinnitus symptoms (Hallam et al., 1984). According to the model, these factors can be the amount of worrying or distress, but also personality traits like neuroticism. Every stimulus that increases the awareness of the tinnitus can increase the perceived suffering and vice-versa everything that leads to a reduction of distress and autonomic system arousal is regarded as beneficial for a relief of symptoms. It is an advantage of this model that these assumptions can easily be applied to tinnitus

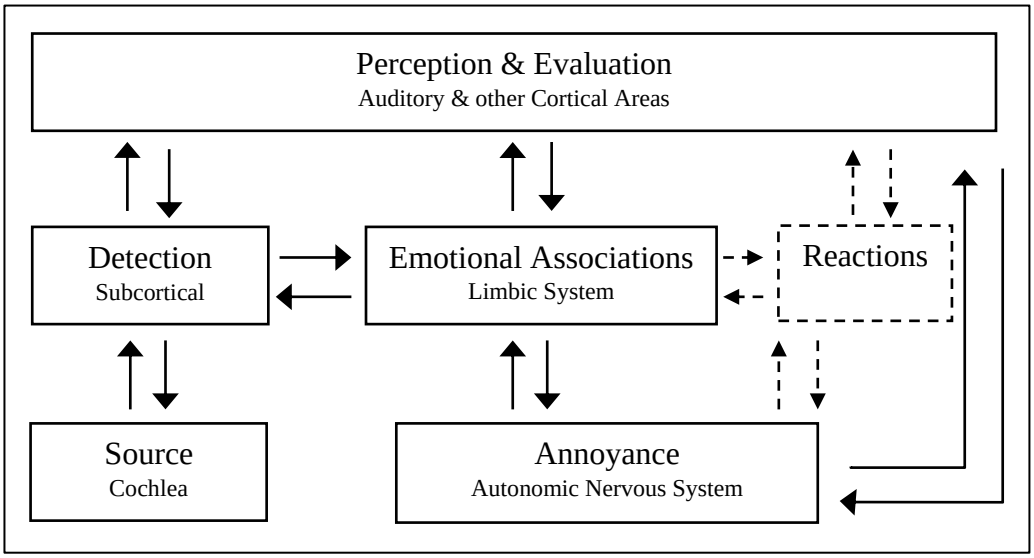
therapy, for example, relaxation therapy as a part of most cognitive behavioral therapy (CBT) protocols. However, none of these psychological treatments abolished the tinnitus tone; rather, they reduced the correlate suffering, indicating that these psychological symptoms are the consequence of an unknown pathophysiology.

The Neurophysiological Model of Tinnitus

According to the neurophysiological model of tinnitus by Jastreboff (1999), the manifestation of tinnitus is perceived as most annoying, when tinnitus is related to the activation of non-auditory brain systems. Particularly, the limbic and the autonomic nervous systems are considered as playing crucial roles in creating distress and tinnitus. Minor imbalances of neural activity in the auditory system, sometimes following a cochlear damage (McFadden, 1982), are detected at lower levels of the auditory system, enhanced by subcortical centers, and then transferred to the auditory cortex where they are perceived as tinnitus. However, when the tinnitus initiated by the auditory system is not reinforced through negative associations (for instance, false information provided by friends or family members about a potential brain tumor) and the tinnitus is treated as natural event, habituation occurs. Thus, the tinnitus sound is perceived but does not lead to discomfort or annoyance. In contrast, when there are negative emotions or beliefs about the tinnitus, the sympathetic nervous system (SNS) can be activated through the limbic system. Catecholamines are released and produce a flight or fight response. Due to the unpleasantness of this response, a negative stimulation loop is initiated (Jastreboff, Gray, & Gold, 1996; Jastreboff, Hazell, & Graham, 1994). This neurophysiological model of tinnitus is depicted in Figure 1.

Figure 1

The Neurophysiological Model of Tinnitus According to Jastreboff (1999)



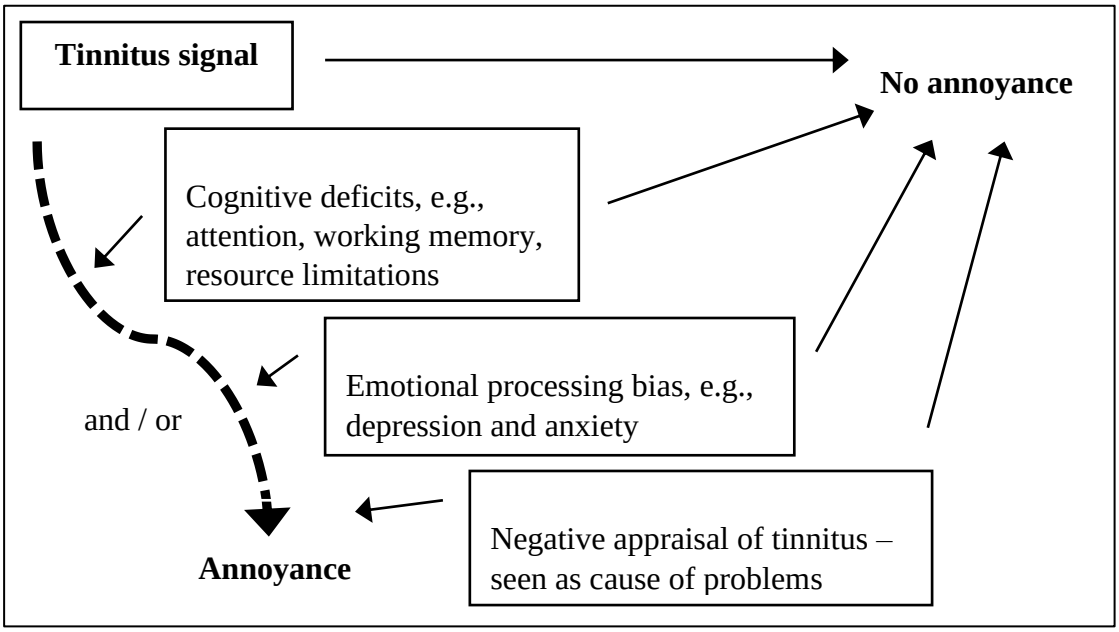
The Cognitive Model of Tinnitus

One of the most popular models of the interaction between tinnitus and cognition was presented by Andersson and McKenna (2006). In their model, three different levels of interaction are discussed: Firstly, based on evidence about the impaired capacity of tinnitus patients to perform certain cognitive tasks, it can be derived that healthy cognitive functioning can be interrupted by tinnitus. The assumption of an effect of tinnitus on cognition is supported by two studies which showed that patients with severe tinnitus were slower in the Stroop task compared to matched control groups with individuals not suffering tinnitus (Andersson, Eriksson, Lundh, & Lyttkens, 2000; Stevens, Walker, Boyer, & Gallagher, 2007). In both studies differences were not attributable to hearing level, anxiety, or depression. A further study revealed that tinnitus patients responded slower in a reaction time task under dual-task conditions (Hallam, McKenna, & Shurlock, 2004) compared to a control group without tinnitus, and also performed worse in the digit-symbol test, a commonly

used neuropsychological test that measures cognitive dysfunction (Lezak, 1995). Secondly, there are indications of tinnitus sufferers showing a certain cognitive bias in handling information. It is suggested that tinnitus patients think in a depressive or anxious manner, or both. While depressive functioning might be related to a memory bias, anxious vigilance could be related to selective attention (Andersson & McKenna, 2006). This assertion of an emotional processing bias was supported by a study, which revealed that compared to a control group, individuals suffering from tinnitus had difficulty retrieving specific memories related to positive cue words in an autobiographical memory test (Andersson, Ingerholt, & Jansson, 2003). Thirdly, if tinnitus is evaluated as a severe issue and as the cause of other serious problems (such as concentration problems and insomnia), annoyance and thus suffering will occur. As shown in Figure 2, on each of the three levels of interaction between tinnitus and cognition, tinnitus annoyance can be intensified. However, there are also routes on each level leading to a reduction of annoyance.

Figure 2

The Cognitive Model of Tinnitus According to Andersson and McKenna (2006)



Synopsis of Tinnitus Models

Although psychological, neurophysiological, and cognitive models of tinnitus emphasize different parts of tinnitus generation and perception, they often complement each other more than they counteract. In particular, the effect of the autonomic nervous system and the limbic system on the perception of tinnitus and its accompanying disorders and symptoms seems to be uniformly assumed. This can explain why certain patients suffer more than others despite equal loudness and why tinnitus is very often associated with specific psychological disturbances.

History of Tinnitus Therapy

Due to the complexity of the involved neural networks as well as the variety of theories about the causes and pathophysiology of tinnitus, treatments of chronic tinnitus are remarkably diverse. Nonetheless, therapy of tinnitus dates back more

than 3600 years; attempts to treat it where already known in old Egypt, ancient Mesopotamia, and by the ancient Greeks (Stephens, 1984). The earliest notations originating from 1600 B.C. were written on papyruses in Egypt and refer to a “bewitched ear” (Stephens, 2000). For therapy, ingestion of desert date oil and frankincense, an ancient universal remedy that comes from the resin of the Boswellia tree, was prescribed. In the later crocodilopis papyruses (second century B.C.), medicines consisting of herbs, salt, and saps of black reed and lotus were also proposed. Even more so than the Egyptian remedies, detailed Assyrian writings included treatment rituals. Prescriptions discovered on clay tablets in the old library of King Assurbanipal (668 – 626 B.C.) in Ninevah (translated by Thompson (1931)) included, for instance, myrrh and cedar fluid. Since tinnitus was described as the ears “speaking”, “whispering”, or “singing” with the involvement of spirits and ghosts, in addition to the instillation of herbs, oils, and liquids in the acoustic meatus, the application of charms and incantations were also advised as treatment (Feldmann, 1997). Furthermore, some therapies were different depending on whether the left or right ear was involved and whether the ear was “speaking”, “whispering”, or “singing”. Unfortunately, it is not known which differentiation the Assyrians meant by these terms, especially when they referred to “speaking”. Treatments of the “whispering” and most treatments of “singing” in the ear were accomplished by incantations varying in length from single words to whole paragraphs (Stephens, 1984).

In contrast to the Egyptian and Mesopotamian writings, the Greek documents which survived focus on theories of tinnitus and hearing rather than on specific treatments (Stephens, 1984). One of the theories, for instance, was that tinnitus was caused by wind being entrapped in the ear. Scripts of the Hippocratic Corpus, a collection of more than 60 texts attributed to Hippocrates (460 – 377 B.C.), illustrate that beating and pulsing of the veins accompanied by deafness was the cause for the

symptoms (Hesse, 2008). More evidence for early treatments was found in the manuscripts of the Roman polymath Celsus, circa 30 A.D. (Hesse, 2008). He mentioned tinnitus in consequence of colds, epilepsy, or headache. As treatment he suggested the cleaning of the ear if the cause of the condition was due to a cold, and dieting, gargling, and herbal ear drops if the symptoms were related to the head. The physician Galen (129 – 199 A.D.) blamed fumes soaring from the stomach and sensitizing the hearing organ as the cause for tinnitus. These reactions were facilitated by an upset stomach due to too much wine, for instance, or the wrong medication. The instillation of mild materials into the ear was regarded as favorable treatment. In medieval times, most physicians still believed in different syntheses of humoral theories. Hence, remedies targeting specific imbalances of humors remained most widely unchanged except for variations related to regional herbs or plants (Stephens, 1984).

One of the few approaches which varied from these therapies was from the prominent French surgeon Guy de Chauliac (1300 – 1370). He recommended for tinnitus patients to take long walks and to find relief by being yelled at and being scared by a screaming voice (Politzer, 1907). Although major advances in anatomical knowledge occurred during the renaissance, it was not until the eighteenth century that major changes related to tinnitus treatment occurred. These innovations were due to the discovery of physiological electricity during that time. Electricity was universally used to cure all kinds of disorders and symptoms, including tinnitus. The first evidence of successful treatments came from Georg Daniel Wibel who reported his attempts in 1768 without a detailed description of the used technique.

In the early nineteenth century, significant contributions came from two physiologists named Jean Marie Gaspard Itard (1774 – 1838) and John Harrison Curtis (1778 – 1860). Itard, a French physician who can be regarded as the father of

audiological medicine, classified tinnitus into two main categories: “true tinnitus” (nowadays described as “objective tinnitus”) when the symptoms are related to internal physiological noises usually due to a vascular anomaly or obstruction of auditory passages and “false tinnitus” (nowadays known as “subjective tinnitus”) when the sound is a phantom percept and is not related to internal physiological stimuli (Baguley et al., 2013a). Both are frequently accompanied by hearing loss. The remedy for “true tinnitus” was based on the objective to treat the obstruction, the vascular anomaly, or the excess of blood in the head. To obtain these goals, irritant footbaths, or bloodletting through the application of leeches on the legs or incision of the great saphenous vein were applied. As a remedy for “false tinnitus”, local or general antispasmodics were his methods of choice. Local antispasmodics were either directed to massages of the head, the auditory meatus, or warm applications of the ear (Stephens, 1984). Itard (1821) admitted the inefficiency of many tinnitus treatments and was one of the first to emphasize the role of physicians to help their patients cope with their symptoms and make their lives more acceptable. One of his proposed techniques to achieve this aim was through masking by means of sounds of water mills, roaring fire, or clockwork motors. Furthermore, he advocated attention to behavioral manifestations like sleep disturbances. The achievement of Curtis, who also founded the Royal Ear Hospital – the first ear hospital in London, was the recognition of psychological aspects of tinnitus and the endorsement of psychological cures involving relaxation and spa treatments. Moreover, he perceived the importance of short-term acute treatments of the tinnitus to limit long-term consequences (Stephens, 1984). During the middle and late part of the nineteenth century, despite major changes in medicine based on advancing technologies such as anaesthesia and asepsis, tinnitus treatments remained rather unaffected by these developments.

In the first half of the twentieth century the method of sound masking continued with advancements from James Spalding, who created one of the earliest therapeutic sound devices in 1928, and Edmund Fowler, who is credited with the first comprehensive attempt to depict the matching and masking characteristics in tinnitus patients in 1941. Despite of the fact that some devoted researchers, including the Polish-American neuroscientist Pawel Jastreboff, the British physician Jonathan Hazell, and the British psychologist Richard Hallam, provided innovations worthy of mentioning, tinnitus was not a main area of interest in the second half of the twentieth century, neither for scientists nor for clinicians (Baguley et al., 2013a).

Modern Treatment of Chronic Tinnitus

Nowadays, there are many treatment approaches available for tinnitus therapy ranging from pharmacological treatments through psychotherapy, sound therapy, non-invasive and invasive brain stimulation, to combined therapies. While some treatments such as brain stimulation techniques target a reversion of the maladaptive reorganization (mainly in the auditory cortex), some other approaches, including psychotherapy, aim to modulate secondary symptoms such as accompanying psychological disorders through a change of cognition and emotions.

Pharmacological Treatments

The efficacy of many drugs to treat chronic tinnitus has been studied including benzodiazepines, non-benzodiazepine anticonvulsants, or tricyclic antidepressants. Yet almost all pharmaceuticals failed to show better effects than placebo (Beebe Palumbo, Joos, De Ridder, & Vanneste, 2015; Dobie, 1999; Langguth & Elgoyhen, 2012; Patterson & Balough, 2006). Pharmacological therapy could only affect tinnitus related psychological comorbidities such as depression or anxiety (Baldo, Doree,

Molin, McFerran, & Cecco, 2012; Langguth & Elgoyhen, 2012). Thus, no drugs are EMA or FDA licensed to be prescribed for tinnitus therapy, except intravenous injection of vasoactive local anesthetics, such as lidocaine, for acute usage. However, the lengths of effectiveness are noticeably short and there are too many risks for long term therapeutic use (Baguley, McFerran, & Hall, 2013b).

Cognitive Behavioural Therapy

CBT is a structured psychological therapy, usually offered on an outpatient basis, that includes psychological techniques like psychoeducation, cognitive restructuring, behavioural activation, and relaxation (Hesser, Weise, Westin, & Andersson, 2011). Originally developed as a therapy for depression, CBT emerged in the mid-80s as a treatment for tinnitus (e.g., Scott, Lindberg, Lyttkens & Melin, 1985) and is now one of the most researched approaches in this field (Hesser et al., 2011). In addition to education about the tinnitus symptoms, tinnitus-specific CBT should take into account the role of significant influencing factors such as otological attention focus or hearing loss, as well as associated motivational-emotional side effects or special avoidance activities (Boecking, Brueggemann, & Mazurek, 2019). The focus of most approaches is on relaxation techniques such as progressive muscle relaxation (Jacobson, 1938) or autogenic training (Schultz & Luthe, 1959). From a psychotherapeutic point of view, it also appears extremely important to orient interventions to individual case conceptualizations that focus on both tinnitus-related distress and broader distress independent of tinnitus (Boecking et al., 2019).

CBT for tinnitus patients has been investigated by a handful of systematic reviews (e.g., Andersson & Lyttkens, 1999; Cima, Andersson, Schmidt, & Henry, 2014; Martinez-Devesa, Waddell, Perera, & Theodoulou, 2007). Although empirical evidence for the efficacy of CBT was provided by all these reviews, efficacy size and

affected outcome variables varied greatly. Andersson and Lyttkens (1999) found medium effects on tinnitus annoyance for controlled studies (*d* = 0.86) and a superiority of CBT (*d* = 1.1) compared to other psychological treatments (*d* = 0.30), whereas Hesser et al. (2011) reported a positive impact on tinnitus-related distress (Hedges *g* = 0.70 and 0.44) and mood (Hedges *g* = 0.42 and 0.35) compared to passive controls (waiting list) respectively active controls (education or pharmacological or other psychological treatments). Less positive findings were yielded by a Cochrane Review in which a medium effect size (*d* = 0.70) of CBT on quality of life compared to passive controls (*d* = 0.64 compared to active controls), but no effects related to subjective tinnitus loudness and depression were found (Martinez-Devasa et al., 2007). This could be due to the restrictive inclusion of randomized controlled trials (RCTs) only, compared to the other reviews. In an update, a significant effect on tinnitus-related distress (*d* = 0.91 compared to passive controls; *d* = 0.64 compared to active controls) and a small but significant impact on depression compared to passive controls (*d* = 0.37) could be demonstrated. Also, a non-significant impact of CBT on subjective loudness could be reported (Martinez-Devesa, Waddell, Perera, & Theodoulou, 2010). Although the efficacy of CBT in tinnitus patients could be clearly demonstrated in these reviews, the effect on important variables such as tinnitus loudness and annoyance caused by the tinnitus is still not documented satisfactorily and should be addressed by future research. Nonetheless, CBT is widely regarded as the gold standard for the treatment of tinnitus (e.g., Andersson & Lyttkens, 1999; Cima et al., 2014; Zenner et al., 2015).

Sound Therapy

In comparison to other attempts to deal with tinnitus, sound-based treatments (e.g., frequency discrimination training, tailor-made notch music training [TMNMT],

and auditory perceptual training) are relatively new. These employ various acoustic backgrounds, hearing aids, or wideband noise generators. Due to their initial effect to distract from the tinnitus, they are also called maskers (Baguley et al., 2013a). These approaches claim that sound-based training not only can mask the perception of tinnitus but also change activity in the central auditory system for tinnitus symptom reduction. Even if the superiority of a purely acoustic mechanism to promote tinnitus remediation is difficult to evaluate (Hoare, Kowalkowski, & Hall, 2012), some treatments could demonstrate to some extent promising results. For instance, by means of TMNMT, a therapy approach where patients are exposed to enjoyable, self-chosen music, with no energy in the frequency bands around their individual tinnitus frequency, a decrease in subjective tinnitus loudness and a reduced neural activity in auditory cortex areas corresponding to tinnitus compared to controls was shown (Okamoto, Stracke, Stoll, & Pantev, 2010; Stracke, Okamoto, & Pantev, 2010; Teismann, Okamoto, & Pantev, 2011). In a more recent TMNMT study, a positive effect on tinnitus loudness was revealed while the level of tinnitus distress did not indicate relevant changes (Stein et al., 2016).

Tinnitus Retraining Therapy

Based on the neurophysiological model of tinnitus (Jastreboff, 1990), tinnitus retraining therapy (TRT) is aimed to increase the patients' habituation to the tinnitus by means of CBT or psychological or non-psychological counseling in combination with sound therapy (Jastreboff, 2007). It is also called the habituation method. TRT has the goal to suppress emotional reactions and negative associations as well as to decrease or eliminate the tinnitus perception at the cerebral cortex level (Jastreboff & Hazel, 1993). The habituation of emotional reactions is achieved through psychotherapeutic techniques, whereas the habituation of perception is

accomplished by means of sound therapy devices. On the neurophysiological level, both processes are related to neuroplasticity (Jastreboff, 2007). Psychotherapeutic techniques aim to decrease the excitation from the cortical areas to the limbic and autonomic nervous systems. Likewise, sound therapy should alleviate the activity in the auditory system and on the following pathways to the limbic and autonomic nervous systems (Jastreboff, 2007). Ultimately, the habituation should facilitate a decreased awareness of the tinnitus so that patients would only perceive it when they are focusing their attention towards it. Albeit positive effects of TRT on tinnitus could be shown in some studies (Bauer & Brozoski, 2011; Henry et al., 2006; Zetterqvist Westin et al., 2011) the quality of most research on TRT seems to be poor (Phillips & McFerran, 2010). Additionally, the efficacy of TRT in the majority of studies could not exceed CBT (Delb, D'Amelio, Boisten, & Plinkert, 2002; Zenner et al., 2015).

Cochlear Implants

Cochlear implants (CIs) are electrical devices which are surgically implanted to restore the hearing function of the cochlea. To date, they are only indicated if the tinnitus is accompanied by a moderate to profound uni- or bilateral hearing loss. However, in addition to their function to restore hearing, it could be shown that they reduce tinnitus. In a review by Quaranta, Wagstaff, and Baguley (2004), a reduction of tinnitus awareness and intensity in up to 86% of the patients was reported. A further review showed an immediate tinnitus suppression after CI intervention in 82% of the patients and a long-term relief of tinnitus symptoms in 45% of the patients (Punte, Meeus, & Van de Heyning, 2011). Incidence of patients with an increase of tinnitus ranged from 0 to 9%. It has to be stressed that bilateral CIs in tinnitus patients not only result in tinnitus suppression (Knopke, Szczepek, Häussler, Gräbel, & Olze, 2017), they are also able to increase health-related quality of life, including a

reduced risk of early onset dementia and cognitive deficits, as demonstrated by prospective studies (Knopke et al., 2017; Olze et al., 2012) and systematic reviews (Berrettini et al., 2011; Claes, Van de Heyning, Gilles, Van Rompaey, & Mertens, 2018).

Bio- and Neurofeedback

Biofeedback allows the patients to learn the voluntary control of vegetative and central nervous physiological parameters by operant conditioning (Miller, 1969). Specific physiological variables like skin conductance or heart rate are displayed acoustically or visually in real time and enable the modification of autonomous function with feedback and learning. Even though biofeedback tends to be superior to most competing tinnitus treatments, the effects of biofeedback of peripheral variables seem to be limited in time and magnitude and cannot outweigh CBT as the gold standard in tinnitus therapy (Ogata, Sekitani, Moriya, & Watanabe, 1993; Podoshin, Ben-David, Fradis, Gerstel, & Felner, 1991).

Following biofeedback, the efficacy of neurofeedback as a tinnitus treatment was also investigated. For this special form of biofeedback, brain signals acquired by brain imaging techniques such as functional near infrared spectroscopy (fNIRS), functional magnetic resonance imaging (fMRI), or electroencephalography (EEG) are used to allow operant control of physiological parameters (Birbaumer, Murguialday, Weber, & Montoya, 2009). Once the patient has learned to control the central auditory activation, this strategy can be applied to everyday life to alleviate tinnitus. Its superiority compared to frequency discrimination training (Dohrmann, Weisz, Schlee, Hartmann, & Elbert, 2007) and transcranial magnetic stimulation (TMS) (Hartmann, Lorenz, Müller, Langguth, & Weisz, 2014) could be demonstrated.

Two EEG-studies, each including 40 patients, could demonstrate a significant reduction in tinnitus-related distress by means of an upregulation of alpha activity (8–12 Hz) and a downregulation of beta activity (14–30 Hz) in tinnitus patients compared to controls (Gosepath, Nafe, Ziegler, & Mann, 2001; Schenk, Lamm, Gündel, & Ladwig, 2005). An enhancement in the alpha band is a sign for increased neuronal inhibition, while a reduction of beta activity can be regarded as a sign of decreased activation. In one of the two studies, the reduction of tinnitus-related distress was shown for all 40 patients 6 months after the end of the study (Gosepath et al., 2001). In contrast to these studies, the investigation of Dohrmann et al. (2007) focused on the downregulation of the delta (1–4 Hz) instead of the beta band due to evidence, that tinnitus patients also show an enhancement in this band compared to normal hearing controls (Weisz, Moratti, Meinzer, Dohrmann, & Elbert, 2005a). Dohrmann et al. (2007) focused on temporal and frontal areas, whereas for Gosepath et al. (2001) and Schenk et al. (2005), the posterior regions were of greater interest. In a pilot study, a beneficial effect of fMRI neurofeedback on tinnitus could be shown in two of six patients (Haller, Birbaumer, & Veit, 2010). The approach used differed substantially from most previous neurofeedback treatment methods due to its focus solely on the auditory cortex BOLD increase: patients had to decrease their blood flow in auditory areas. A novel EEG setup was developed by our research group, published (Malekshahi et al., 2020), and also plays an important part in the dissertation of Azim Malekshahi. For details, see appendix I. The approach aims to increase auditory cortex alpha activity solely. It enables the simultaneous suppression of visual and somatosensory alpha power through visual stimulation and air flow as tactile face-stimulator. Another novelty of the setup is the inclusion of pink noise, also known as 1/f noise, as an acoustic tinnitus masker.

However, aside from all encouraging results, it has to be noted that many neurofeedback studies lack a comparison-group, that there are issues in respect to technological aspects of the imaging methods, such as the limited spatial precision of EEG, and that protocols are often heterogenous. Future research on neurofeedback is necessary to establish different neurofeedback protocols for given subgroups of tinnitus patients or even to develop individualized protocols for each patient. Furthermore, for an effective therapy, domains and measurements are needed to be able to separate responders from non-responders.

Non-Invasive Brain Stimulation

Based on the finding that tinnitus is linked to high spontaneous neural activity in the auditory cortex and associated areas (Arnold, Bartenstein, Oestreicher, Römer, & Schwaiger, 1996; Eggermont & Roberts, 2004; Mühlnickel, Elbert, Taub, & Flor, 1998), transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) have also been investigated as tinnitus treatments. TDCS is a non-invasive neurostimulation technique that uses constant direct current provided through electrodes on the scalp. A combined therapy of TMNMT and anodal or cathodal tDCS with an active electrode placed over the left auditory cortex and a reference electrode placed over the right supra-orbital cortex demonstrated positive treatment effects. It did not make a difference, however, whether anodal or cathodal tDCS was applied, and the efficacy was not superior to TMNMT and sham stimulation (Teismann et al., 2014).

TMS is a non-invasive method using electromagnetic induction to stimulate specific brain areas. The excitability of neurons in particular brain areas can be modulated to decrease the hyper-excitability that is associated with tinnitus emergence thorough low frequency stimulation (below 5 Hz) (Kleinjung, Steffens,

Londero, & Langguth, 2007). A short-time reduction in tinnitus loudness following a left temporoparietal 10 Hz rTMS that induced a “virtual” lesion (excitation) could be demonstrated (Plewnia, Bartels, & Gerloff, 2003). Similar results could be shown using a temporoparietal 1 Hz low-frequency rTMS (Plewnia et al., 2007a). Moreover, a tinnitus suppression in about 50% of the participants using high-frequency rTMS at the temporo-parietal area could be reported in several studies (De Ridder et al., 2005; Folmer, Carroll, Rahim, Shi, & Hal Martin, 2006; Fregni et al., 2006). However, often tinnitus perception could be modified only for a very short time and the safety of long-term use is not established yet. Therefore, further trials are needed before TMS can be regarded as an option for routine usage (De Ridder et al., 2005; Langguth et al., 2008; Meng, Liu, Zheng, & Phillips, 2011).

Invasive Brain Stimulation

As one of the most recent treatment approaches for tinnitus, invasive brain stimulation includes promising techniques such as deep brain stimulation (DBS) and intracranial auditory cortex stimulation (Vanneste & De Ridder, 2012). DBS for subcortical brain areas has emerged as a highly successful treatment for therapy-resistant disorders including Parkinson’s disease, chronic pain, and dystonia, and is also emerging for psychiatric diseases such as depression, obsessive-compulsive disorder, and epilepsy (Miocinovic, Somayajula, Chitnis, & Vitek, 2013). Unfortunately, there are no DBS studies primarily targeting tinnitus; yet evidence for the efficacy of DBS is coming from studies primarily focusing on other disorders. Seven patients with movement disorder and accompanying tinnitus underwent an implantation in the ventralis intermedius nucleus in the thalamus. Three of the seven patients (43%) reported reduced tinnitus loudness during the stimulation (Shi, Burchiel, Anderson, & Martin, 2009). Furthermore, six patients with Parkinson’s

disease and comorbid tinnitus received an implant in the subthalamic or ventralis intermedius nucleus in the thalamus which led to a suppression of tinnitus loudness in five of the six patients (83%) (Cheung & Larson, 2010).

In intracranial auditory cortex stimulation, an electrode controlled by an internal pulse generator implanted subdermally in the abdomen is placed supradurally at the secondary auditory cortical area to achieve a permanent modulation (Vanneste & De Ridder, 2012). Initial results using tonic stimulation revealed that patients with pure tone tinnitus benefited from this therapy while patients with noise-like tinnitus did not (De Ridder et al., 2006). Patients having a tinnitus that combined both components did not profit either. In a comparison study between burst stimulation and tonic stimulation in five tinnitus patients with an implanted electrode on the auditory cortex, a better suppression of narrow-band noise tinnitus was shown for the burst stimulation. (De Ridder et al., 2010). Likewise, burst stimulation was superior to tonic stimulation in 43 patients with severe tinnitus who had a cortical electrode implanted on the secondary auditory cortex (De Ridder et al., 2011). Initially, all patients reacted to TMS, whereas only 67% responded to cortical stimulation. The average tinnitus reduction for the entire group using cortical stimulation was 53%.

Discussion

In spite of the fact that there is progress in some areas of tinnitus research, it should be stressed that there are still many gaps in our knowledge. The two essential questions regarding tinnitus remain unanswered: What is the cause for tinnitus? And how can it be successfully and causally treated? With regard to the existing tinnitus models, it can be concluded that even if they are not able to identify the ultimate cause for tinnitus, they can at least describe the role of different brain areas in determining the relationship between perceived tinnitus loudness and psychological

distress, and hence predict why some patients may suffer more than others. With respect to therapy, the important question is whether future methods will be able to overcome the problem that unlike secondary outcome variables such as quality of life, tinnitus sound remains widely unaffected by traditional therapies. Cochlear implants can be regarded as an effective therapy but are to date only indicated if the tinnitus is accompanied by a profound hearing loss and should therefore not be regarded as a universal remedy. However, it remains to be seen if and when this will change resulting in CIs being indicated if the quality of life is seriously comprised but not the hearing ability. The most established therapy approach is still CBT but neurofeedback and invasive as well as non-invasive neuromodulation techniques, such as DBS or rTMS are on the rise. Nevertheless, also for these approaches stronger evidence of the efficacy and randomized clinical trials are needed to allow characterizing them as effective treatments.

However, the comparison of tinnitus treatments across clinical trials is often restricted by outcome measures. In their systematic review, Hall et al. (2016) observed a broad diversity of methods to measure the efficacy of tinnitus treatments and in many studies primary and secondary outcome domains were unclear and not described adequately. A tinnitus attribute that is frequently used is loudness, but there is no consensus on how to measure it and often the methodology is not reported precisely. This argument of a variety of outcomes also applies to tinnitus self-evaluation questionnaires such as the Tinnitus Handicap Inventory (THI; Newman, Jacobson, & Spitzer, 1996), which is most popular, and the Tinnitus Handicap Questionnaire (THQ; Goebel & Hiller, 1994). Another point of criticism for the authors is the request for a record of not only benefits but also harms. Side-effects, tolerability, and safety are often described poorly but a detailed report would be necessary to evaluate the efficacy of tinnitus treatments (Hall et al., 2016).

Summarizing, Itard's assertion from 1821 that "treatment of tinnitus is generally unsuccessful and in most cases the physician's orientation must be towards the relief of disturbing symptoms" (Stephens, 1984, pp. 970) remains even nowadays for the greater part true. To develop effective treatments, a more interdisciplinary cooperation between neuroscience, otolaryngology, physiology, and psychology is mandatory – if not for the patients' cure from symptoms, then at least for a relief of their suffering.

Chapter Two: Experimental Study – Neural Correlates of Chronic Tinnitus and Psychological Disorders

Introduction

According to epidemiological studies, 14 to 80% of people suffering from tinnitus are affected by depression, in contrast to 7 to 9% in non-tinnitus control-groups (Bhatt et al., 2017; Stobik et al., 2005; Sullivan et al., 1988; Zöger et al., 2001). Reason for this large variability could be different sample recruitments and/or different diagnostic criteria for depression. The same applies to (a lesser degree) to anxiety disorders, by which 19 to 45% of tinnitus patients are affected in comparison to around 9% in controls not suffering from tinnitus (Bhatt, et al., 2017; Belli et al., 2008; Marciano et al., 2009; Zöger et al., 2001). The prevalence of sleeping problems in tinnitus patients ranges from 50 to 77% (Alster, Shemesh, Ornan, & Attias, 1993; Axelsson & Ringdahl, 1989; Folmer & Griest, 2000; Hallam, 1996).

Suffering in tinnitus patients is not only dependent on the loudness and the pitch of the tinnitus (Hazell et al., 1985; Rachman & Philips, 1980). Nor does variability, localization, discomfort threshold or the etiology of the tinnitus seem to have a crucial influence on the amount of suffering (Kratzsch & Goebbel, 2018). In fact, besides changes within the central auditory pathway (Eggermont & Roberts, 2004; Giraud et al., 1999; Kaltenbach, 2006; Weisz et al., 2005a), the involvement of non-auditory brain structures like the limbic system, the reticular formation, or the sympathetic autonomic nervous system seems to be the crucial factor for the decreased quality of life of severely affected tinnitus patients (Jastreboff et al., 1994; Weisz et al., 2007a; Weisz et al., 2005a).

These results are in line with positron-emission tomography (PET) studies showing that tinnitus sufferers not only have an increased metabolic activity in the

primary auditory cortex (Arnold et al., 1996; Eichhammer, Langguth, Marienhagen, Kleinjung, & Hajak, 2003) but also in non-auditory brain systems such as the limbic system, anterior midline structures, and the prefrontal cortex (Lockwood et al., 1998; Mirz et al., 1999; Mirz, Gjedde, Stödkilde-Jörgensen, & Pedersen, 2000). Weisz et al. (2005a) could reveal a marked reduction in the alpha (8–12 Hz) band and an enhancement in delta (1.5–4 Hz) power of tinnitus patients compared to normal hearing controls. Correlations with tinnitus-related distress showed a strong link to this abnormal spontaneous activity pattern, particularly in left frontal and right temporal areas. A meta-analysis that included nine PET, single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI) resting-state neuroimaging studies identified increased resting-state brain activity of tinnitus patients relative to controls in the insula, middle temporal gyrus (MTG), parahippocampus, cerebellum, and frontal cortex. A decreased brain activity was reported for the cuneus and thalamus (Chen et al., 2017). These findings indicate the link between tinnitus and various brain subnetworks including memory, salience, and attention. However, there is no theoretical framework capable of explaining all these aspects in one comprehensive model.

Similar results were found with quantitative electroencephalography (QEEG) studies. Positive neuronal correlates of tinnitus severity were observed in the delta (0.5–3.5 Hz) and beta (13.5–22 Hz) frequency in temporal and frontal regions (Shulman, Avitable, & Goldstein, 2006; Shulman & Goldstein, 2002). Delta activity may reflect a deprivation of (thalamic) input in cortical neurons, whereas beta represents intracortical interactions with input from all afferent sensory pathways. These intracortical interactions can result in a reduction of the GABAergic influence of the reticular thalamic nucleus (Shulman et al., 2006). A resting-state study showed an overactivity of delta (2–4 Hz), theta (4–8 Hz), and beta (18–25 Hz) in tinnitus

patients compared to healthy controls (Moazami-Goudarzi, Michels, Weisz, & Jeanmonod, 2010). Using LORETA source analysis, the generators were localized predominantly to left auditory (Brodmann Areas (BA) 41, 42, and 22), anterior cingulate, temporo-parietal, parahippocampal, and insular posterior cortical areas. According to some authors (e.g., Jeanmonod, Magnin, & Morel, 1996; Moazami-Goudarzi et al., 2010), these results are pointing towards a thalamocortical dysrhythmia at the source of tinnitus. The thalamocortical dysrhythmia is hypothesized as the result of a resonant interaction between thalamus and cortex due to the formation of low-threshold calcium spike bursts in thalamic cells. The occurrence of these bursts is causally linked to thalamic cell hyperpolarization (Jeanmonod et al., 1996; Llinás, Ribary, Jeanmonod, Kronberg, & Mitra, 1999). In a healthy person, surround inhibition following thalamocortical input would be expected to constrain synchronous activity to neurons syntonic to characteristics of the acoustic stimulus, thus leading to a normal auditory perception. Yet, when the restraints of intracortical inhibition are attenuated, distributed synchronous activity could develop and stabilize across wider cortical areas which leads to the perception of sounds in absence of a corresponding acoustic source – tinnitus (Eggermont & Roberts, 2004).

With regard to the link between tinnitus and mood disorders, several studies support the theory that a hyperresponsiveness of the limbic system plays an important role in formation and maintenance of tinnitus, depression, and anxiety (Etkin & Wagner, 2007; Langguth, Landgrebe, Kleinjung, Sand, & Hajak, 2011; Lockwood et al., 1998). This hyperreactivity might be subcortically caused by some changes of serotonin synthesis in the raphe nucleus and the locus coeuruleus, which are also implicated in the control of attention and emotions (Kaltenbach, 2006). Research could show that fusiform cells in the dorsal cochlear nucleus (DCN) are

targeted by overactive locus coeruleus-efferent projections, and that this pathway is also involved in the onset and modulation of tinnitus (Kaltenbach, 2006; Pattyn et al., 2016). Furthermore, the correlation between tinnitus and mood disorders was discussed in two reviews which demonstrated similarities in neuroendocrine function in the hypothalamus-pituitary-adrenal (HPA) axis with respect to tinnitus and depression (Langguth et al., 2011), and an increased cortisol release and a reduction in GABA transmission with respect to tinnitus and anxiety (Pattyn et al., 2016). On a neuronal level, correlations between depressive symptoms measured by the BDI and an increased alpha activity in the left frontopolar cortex (FPC), the left orbitofrontal cortex (OFC), and over the subgenual anterior cingulate cortex (sgACC) was shown in tinnitus patients (Joos, Vanneste, & De Ridder, 2012; Vanneste, Joos, Langguth, To, & De Ridder, 2014) using sLORETA analysis (Pascual-Marqui et al., 2002). Albeit the difficulties of EEG to measure subgenual activity are known, these results are supported by a fMRI study which showed that the activation in the left dorsolateral prefrontal cortex (dlPFC) and the left medial frontal pole (mFP) increased following sadness induction mediated by the sgACC as interposed area (Ramirez-Mahaluf, Perramon, Otal, Villoslada & Compte, 2018).

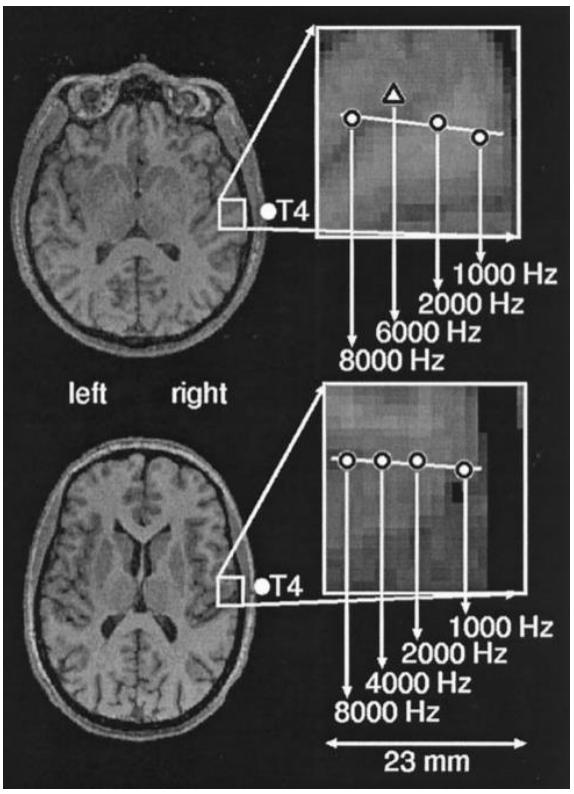
Since it is indicated that the OFC is part of the reward system (Kringelbach, 2005), Schlee, Mueller, Hartmann, Keil, Lorenz, and Weisz (2009b) speculate that it could also be responsible for the integration of the aversive information of the perceived tinnitus. Together with the sensory systems, the frontal and the cingulate cortex activity could support the model of the global neuronal workspace as generally proposed by Dehaene and colleagues (Dehaene & Changeux, 2004; Dehaene, Changeux, Naccache, Sackur, & Sergent, 2006), and applied to tinnitus by Schlee et al. (2009b). According to this model, two conditions are required to form a conscious perception of stimuli: neuronal activity of the cortical representation and an entry into

the global neuronal workspace through long-range cortical coupling between the broadly distributed workspace neurons. Coupling within this fronto-parietal-cingulate network is needed for the conscious perception of the stimulus. Sensory cortices are influenced top-down by the global workspace leading to an amplification of the neuronal activity within the respective sensory area. Activity in sensory areas without this coupling would be unconscious.

The reported studies do not allow for a clear conclusion about the functional neuropathology of tinnitus, except that in comparison to healthy controls many cortical and subcortical brain areas involved in the processing of negative emotions and stress are changed in tinnitus patients. Yet, it is unclear whether this is specific and causally responsible for tinnitus or just an unspecific correlate of the stress and helplessness generated by the phantom noise. The EEG data are even more incongruent, except that they also show various pathologies in comparison with healthy controls, thus they do not allow separation of specific and unspecific factors. The only more specific result seems to consist of a distortion of the representation of the tinnitus tone of the regular tone representation on the primary auditory cortex found in a magnetic source imaging (MSI) study by Mühlnickel et al. (1998) with 10 tinnitus patients and 15 healthy controls. Here the tinnitus tone representation shows a marked shift outside the regular frequency area into an area adjacent to the expected tonotopic location (Figure 3). Furthermore, the results imply that the amount of cortical reorganization in individuals suffering with tinnitus is not correlated with the amount of mild to moderate hearing loss, which was also shown by Rajan (1998), but rather with the perceived strength of the tinnitus. These findings of an altered tonotopic organization in tinnitus patients prompt an analogy with a study showing the relationship between phantom limb pain and reorganized somatotopic maps in human amputees (Flor et al., 1995).

Figure 3

Typical Example of the Tonotopic Map for a Left-Sided Tinnitus (Upper) and a Control Subject (Lower) According to Mühlnickel et al. (1998)



Note. Equivalent current dipoles evoked by auditory stimulation at three standard and the tinnitus frequency in the tinnitus patient and four standard frequencies in the healthy control subject are superimposed onto an axial slice of BA 41 (primary auditory cortex) of the right hemisphere. In the upper part of the figure, the line shows the trajectory of the dipole positions of the three standard tones which are depicted as circles. The triangle represents the position of the tinnitus frequency (6,000 Hz in this instance). The four circles and the line in the lower portion of the figure show that the trajectory of the dipole positions of the standard frequencies in the healthy control subject is linear, whereas the dipole of the impacted frequency in the tinnitus subject (upper part) diverges from the linear trajectory constituted by the three standard

frequencies. The location of T4 (according to the international 10–20 system) as well as the scale of measurement are marked.

According to auditory plasticity theory, these cortical alterations are caused by damage to the cochlea which leads to a decreased afferent input into the central auditory system (Pantev et al., 2012). In the auditory cortex in regions adjacent to the region that is deprived of input, sound representations are enlarged. This results in an increased responsiveness of neurons deprived of thalamocortical input towards frequencies adjacent to the regions that represent the frequencies where hearing is disturbed through lateral connections of the apical dendrites (Eggermont & Roberts, 2004; Weisz et al., 2007a; Weisz et al., 2007b). This process of plastic reorganization also generates hyperactivity and therefore an initial tinnitus signal in the ascending auditory pathways. Normally, the limbic system identifies this unwanted auditory signal and eliminates it from perception (“tunes it out”) by feeding it back to the (inhibitory) thalamic reticular nucleus (TRN), which subtracts it from the afferent acoustic signal. Thus, this circuit serves as a neural “noise-cancellation” mechanism. In cases in which the relevant limbic regions become dysfunctional, noise cancellation does not function anymore, and the tinnitus signal permeates to the auditory cortex, where it becomes conscious and eventually leads to the permanent auditory cortical reorganization process (Rauschecker, Leaver, & Mühlau, 2010).

Since all the experimental comparisons of tinnitus patients used healthy controls, a clear hypothesis for a specific cause-effect physiopathology between cortical reorganization and cerebral changes is difficult. Thus, we decided to select clinically highly deviant patients with tinnitus from the less deviant ones, thereby avoiding many of the problems of comparisons between healthy controls. The two

groups we selected are comparable in the nature of their major symptoms, age, and psychopathology; the criterion for their distinction is the experienced severity of the tinnitus tone itself. Because (nearly) everybody has experienced a tinnitus tone once or several times in their life, tinnitus itself cannot be regarded as a clinically relevant phenomenon with a persistent pathophysiology. Only the persistent and highly aversive tone leading to severe suffering can be regarded as a relevant clinical pathology and should be manifested in a clear neurophysiological change responsible for the phantom experience. We are aware of the fact that even in such a comparison, the effects of the unspecific stress caused by the tinnitus cannot be completely separated from the perceptual phenomenon, since such a separation would need a longitudinal study of patients before and after severe tinnitus suffering. Such a study is not possible at present because we do not know the risk factors predisposing a person to tinnitus suffering.

However, from the many retrospective clinical reports of patients, except for a stressful life experience as a first environmental risk factor, no consistent psychopathology or neuropathology is obvious. Thus, we tend to assume that the specific neurophysiological and neuropathological changes of phantom tone perception are the cause, and the psychological aberrations and suffering are the consequences of the unknown pathophysiological or neuropathological causal agent of this phenomenon. Whatever this phenomenon may be, it can be deduced from the literature that a lack of inhibition and/or overexcitation of auditory neurons in the primary and secondary auditory cortices are an important factor in the chain of pathological processes. Overall, severe tinnitus should show signs of one or both of these changes in excitation which should be non-existent or less expressed in people with less severe symptoms but otherwise comparable characteristics. In this study only spontaneous resting state EEG was measured, however, EEG has a notoriously

bad resolution at the level of the auditory cortex hidden behind the temporal cortex convolution. Thus, if at all, only the associated frontal structures may reflect these changes.

The aim of the current study is to investigate if patients suffering severe tinnitus show a different neural activity compared to non-severe tinnitus patients. The tinnitus patients were assigned to two groups: individuals with severe tinnitus and those with non-severe tinnitus according to the accepted international criteria. Their EEG resting state activity was compared. It is suggested to find differences in both the power in both auditory and associative/paralimbic areas. If we assume a disorder of excitation-inhibition balance in the central auditory system and its associated areas, we would expect a topographically specific change at fronto-central electrodes projecting from the auditory cortex in the severe disorder compared to the less dramatic cases. Because depression and anxiety on a subjective-clinical level are the main psychological differential criteria for severity, together with the subjective tinnitus loudness, their contribution is analyzed and it is hypothesized that the depression and anxiety factor is mainly expressed outside the primary auditory cortex in prefrontal, orbitofrontal, and the connected subgenual cortices that are also markers of tinnitus severity. Since subgenual structures are located inaccessible to surface electrodes, their activity may also be visible mostly in medial prefrontal structures in the EEG recordings and topographical analysis.

Materials and Methods

Every assessment was comprised of a 64 electrode EEG eyes-open resting state session plus the implementation of several self-report questionnaires targeting the impact of tinnitus on daily living and different components of the tinnitus patient's quality of life and possible psychological comorbidities. The study protocol was

approved by the Ethical Committee of the University of Tübingen. Written informed patient consent to perform this study was obtained from all participants according to the declaration of Helsinki.

Participants

The sample for this study, which took part at the Institute for Medical Psychology and Behavioural Neurobiology Tübingen between May 2017 and December 2019, consisted of 37 male and female tinnitus patients aged between 18 and 85 years which had non-pulsatile tinnitus for at least 6 months and functional hearing. The study was announced through the mailing list of the university and at the ENT (Eye-Nose-Throat) clinic at the University of Tübingen where patients from the area visit the tinnitus ambulance. Individuals with objective or pulsatile tinnitus, otosclerosis, Ménière's disease, or neurological disorders were excluded from the study. All patients saw an audiologist. Audiometric tests, including hearing threshold and frequency and minimum masking level of the tinnitus, were obtainable for most of them. In addition to EEG measurement and questionnaires, all tinnitus patients were interviewed to receive further information about demographic variables as well as the origin, environmental correlates, location, and characteristics of their tinnitus.

As the data of 3 patients could not be included because of a strong contamination of muscle activity and head movement, the final sample comprised 34 subjects. The age of the total sample of 23 males (67.6 %) and 11 females (32.3 %) ranged from 19 to 83 years (M = 50.1; SD = 16.8). The patients had an average of 16.96 years of education (SD = 2.89). Twenty-six patients had bilateral tinnitus, 4 patients had unilateral left-sided tinnitus, and 4 patients had unilateral right-sided tinnitus. On average, the patients had tinnitus for 10.4 years (SD = 9.4). They rated the overall subjective intensity at 5.4 (SD = 1.3; the max. of 10 means worst) the left-

sided subjective intensity at 5.5 (*SD* = 1.6), and the right-sided subjective intensity at 5.4 (*SD* = 1.6).

Questionnaires

Demographic variables and tinnitus characteristics. Demographic data (sex, age, and education) and various aspects of the tinnitus perception including tinnitus duration, laterality, overall subjective intensity, and subjective intensity per side were collected.

Tinnitus Handicap Inventory. Subjective tinnitus symptoms were measured through the THI (Newman et al., 1996). The THI is a widely used 25-item self-report measure that can be used to assess the impact of tinnitus on daily living. THI results can also be interpreted in terms of the amount of tinnitus distress or handicap caused by tinnitus. In detail, disorders in the areas of mental, physical, and social functioning, affective reactions to tinnitus, and catastrophic responses to the symptoms of tinnitus are gathered. For each item (e.g., “Does your tinnitus make you feel insecure?”), the subject has to choose between “yes” (4 points), “sometimes” (2 points), and “no” (0 points). The total score is then calculated by summing all responses and ranges from 0 to 100. Higher scores denote a larger handicap. A THI score of 0-16 indicates "no or slight handicap", 18 to 36 means “mild handicap”, 38 to 56 represents a "moderate handicap", and a score of 58 to 100 denotes a “severe handicap”. The THI is psychometrically robust and can easily be administered (Newman, Sandridge, & Jacobson, 1998).

Beck Depression Inventory. To detect depressive symptoms, the Beck Depression Inventory II (BDI-II; Hautzinger, Keller, & Kühner, 2006) was used. The BDI-II is an established 21-item instrument for individuals aged between 13 and 80 which ascertains on a 4-point Likert scale how often a subject felt within the past 2

weeks (e.g., “I feel I may be punished” or “I am disgusted with myself”). The items are focusing on cognitive, affective, somatic, and behavioural aspects of depression and are denoted with 0 to 3 points. Higher scores represent more severe depressive symptoms. Scores from 11 to 17 of the maximum score of 63 are increased and indicate mild to moderate depressive symptoms, while scores above 17 refer to clinically relevant depressive symptoms (Hautzinger, Keller, & Kühner, 2010).

State and Trait Anxiety Inventory. The STAI (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983) is a widely used self-report measure to investigate anxiety which has been translated in over 39 languages. The original STAI called STAI-X was first published in 1970. Based on this instrument, the STAI was revised in 1983 with the current form STAI-Y. It consists of two 20-item parts of which one is targeting how the person feels at that moment, called state anxiety (STAI-S or STAI Y1) (e.g., “I feel nervous”), and one is targeting how the person generally feels, called trait anxiety (STAI-T or STAI Y2) (e.g., “I am a content person”). For each item of both parts, the respondents are asked to rate themselves on a 4-point Likert scale ranging from “not at all” to “very much” given a weighted score of 1 to 4. Thus, both scores can vary from a minimum of 20 to a maximum of 80, whereby higher scores indicate greater anxiety. STAI-S and STAI-T scores of 20 to 37 commonly refer to “no or low anxiety”, scores of 38 to 44 represent “moderate anxiety”, and scores from 45 to 80 denote “high anxiety” (Kayikcioglu, Bilgin, Seymenoglu, & Deveci, 2017). Relating to reliability, a review acknowledged the STAI both acceptable internal consistency and acceptable test-retest reliability (Barnes, Harp, & Jung, 2002).

Pittsburgh Sleep Quality Index. The PSQI (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) is a standardized self-report questionnaire to assess sleep quality. It has 19 items (e.g., “During the past month, what time have you usually gone to bed at night?”) plus 5 questions answered by the bed partner or roommate

(which are not included in the scoring), and generates one global score plus seven component scores: sleep quality, sleep latency (time that it takes to fall asleep), sleep duration, habitual sleep efficiency (percentage of bedtime that one is asleep), sleep disturbances, use of sleep medications, and daytime dysfunction. Each component score is ranging from 0–3 points. A score of “0” indicates no difficulty, whereas a score of “3” indicates severe difficulty. The global score is then calculated by adding the seven component scores, providing an overall score with a range of 0–21 points. Global scores ≤ 5 refer to “good sleepers”, whereas global scores > 5 indicate “poor sleepers” (Buysse et al., 1989). The PSQI’s internal consistency reliability and construct validity can be regarded as acceptable to good (Carpenter & Andrykowski, 1998).

Subgrouping of the Tinnitus Patients

The first assignment was based on the tinnitus severity. Patients were assigned to a category according to their THI total score: Non-severe tinnitus symptoms (THI 0–56) and severe tinnitus symptoms (THI 57–100). Following this classification, 9 individuals were included in the severe tinnitus group and 25 in the non-severe tinnitus group. The two groups did not differ significantly regarding their age and tinnitus duration. Yet, the severe tinnitus group had a significantly higher BDI ($t(32) = 2.55$; $p = .015$) than the non-severe tinnitus group. The STAI-T ($t(32) = 1.95$; $p = .059$) and the PSQI ($t(32) = 1.81$; $p = .079$) did not reach significance.

To classify the tinnitus patients with and without mood disorders, we used the following scoring system based on the common classification systems of Hautzinger et al. (2010) for depression and of Kayikcioglu et al. (2017) for anxiety: Patients with BDI scores < 11 gained 0 points, BDI scores of 11 to 17 represent 1 point, and BDI scores > 17 obtain 2 points. In a similar way, STAI-T scores < 37 receive 0 points,

STAI-T scores from 38 to 44 ascertain 1 point, and 2 points are noted for scores > 44. Then, the two scores are summed.

Hence, individuals can gain between 0 and 4 points, whereby total scores of 2 or higher indicate symptoms of mood disorders or anxiety. Using this classification, 16 patients were included in the depression and/or anxiety group, and 18 in the no depression or anxiety group. The two groups did not differ significantly regarding their age and tinnitus duration. With respect to tinnitus severity and sleep problems, the depression and/or anxiety group had a significantly higher THI ($t(32) = 2.34$; $p = .025$), but the PSQI did not reach significance level ($t(32) = 1.88$; $p = .069$).

Behavioural Data Analysis

To investigate the relationship between tinnitus intensity, tinnitus duration, THI, BDI, STAT-T, and PSQI, correlation analysis was done using Pearson correlation. All *p*-values were corrected using the Benjamini and Hochberg (1995) method.

EEG Acquisition and Preprocessing

Subjects were seated on a comfortable chair in a quiet room. The EEG was collected using 64 high-quality Ag/AgCl electrodes, placed with a standard cap using the Brain Products recording system (BrainAmp). To monitor vertical and horizontal eye-movements, three electrodes were placed infra-orbital and supra-orbital to the right eye and 1cm lateral to the left outer canthus. For the eye movement calibration run, the patients had to follow a cue with their eyes, 5 times up and 5 times down and then 5 times to the right and 5 times to the left, in order to specify a threshold for vertical and horizontal eye movements for offline and online rejection of EEG data.

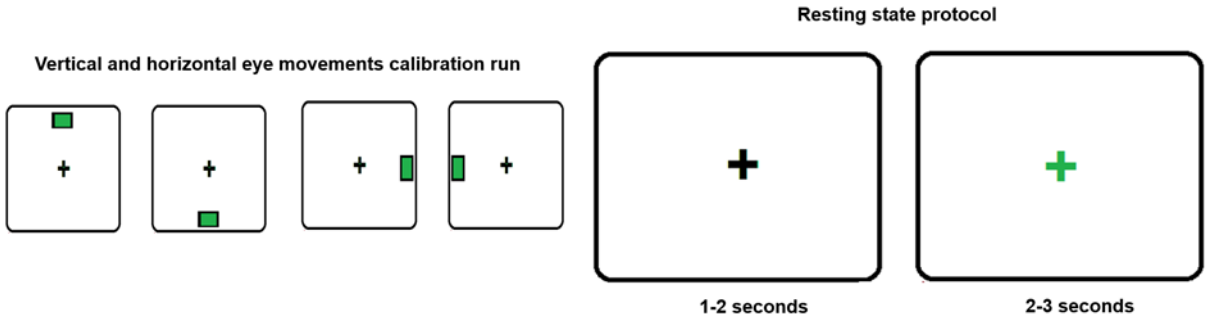
Ten minutes eyes open resting state EEG data was recorded at a sampling rate of 500 Hz. The resting state protocol included 100 trials: each lasting for 1–2

seconds and followed by 2–3 seconds of inter-trial interval. During each trial, the patient focused on a black cross at the center of the screen and was only allowed to blink after a green cross appeared at the center of the screen (Figure 4).

EEG data was offline re-referenced to common average reference and filtered between 1 to 48 Hz to remove possible low frequency noise. Horizontal and vertical eye movement signals in each trial (1 sec) were calculated, and each value in each time point of these signals was compared to the absolute maximum values (AMV) of the eye movement calibration runs for both vertical and horizontal eye movements. If the 0.3 portion of the vertical or horizontal eye movement signal was larger than the AMV, the trial was rejected. Then, the EEG data was visually inspected to remove noisy trials or channels contaminated with muscle activity.

Figure 4

Eye Movement Calibration and Resting-State Protocol



Note. In the eye movement calibration run, the patients had to follow the green square in the vertical direction with their eyes (5 times up and 5 times down). The same procedure was done in the horizontal direction (5 times to the right and 5 times to the left). The resting state protocol includes 100 trials. For each trail, the patient had to focus on the black cross in the middle of the screen for 1–2 seconds, then a green cross appeared, announcing that the patients were allowed to blink for 2–3 seconds.

Power Spectral Analysis

The absolute power spectral density for each channel and EEG segment was computed by using multitaper fast Fourier transform (Percival & Walden, 1993) with 3 tapers. Power spectral analysis was performed using the Fieldtrip toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2011). For statistical analysis, the total frequency range (1–45 Hz) was reduced into five frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–12Hz), beta (12–25 Hz), and gamma (25–45Hz). For every trial with each subject and channel, the power spectrum was calculated and averaged over all channels. Then, the frequency spectra for non-severe tinnitus symptoms and severe tinnitus symptoms were depicted. Based on the first subject assignment, the absolute power for the five mentioned frequencies for the non-severe tinnitus group and the severe tinnitus group was calculated. Independent *t*-tests between the two groups were applied for each frequency band. *P*-values were corrected using the Benjamini and Hochberg (1995) method. The same spectral analysis was done for the second assignment into depression and/or anxiety versus no depression or anxiety.

Source Localization Method

Standardized low-resolution brain electromagnetic tomography (sLORETA; Pascual-Marqui et al., 2002) was applied on cleaned EEG data to estimate the intracerebral active sources generating the scalp-recorded electrical activity in the same five frequency bands. As a standard procedure, a common average reference transformation is used before applying the sLORETA algorithm. The volume conduction model of the template MRI of Fieldtrip data set is calculated on the basis of the boundary element method (De Munck, Wolters, & Clerc, 2012). To compare voxel-by-voxel the current density amplitudes between the two groups in five frequency bands, we used the cluster-based test statistic (Maris & Oostenveld, 2007). The

significance was calculated by means of the Monte Carlo method with 1000 numbers of randomization. This analysis was applied to both assignments of the patients, firstly to non-severe tinnitus symptoms versus severe tinnitus symptoms, and then to depression or anxiety versus no depression or anxiety.

Results

Behavioural Measures

The THI scores of the 34 tinnitus patients ranged from 8 to 100 with a mean score of 40.16 (*SD* = 22.35). By means of the established classification scale, 6 patients (17.7 %) were classified having “no or slight handicap”, 11 patients (32.4 %) were classified having a “mild handicap”, 8 patients (23.5 %) were classified having a “moderate handicap”, and 9 patients (26.5 %) were classified having a “severe handicap”. On the BDI, the patients scored on average 11.00 points (*SD* = 11.82; range from 0 to 58). Using the established cutting score, 22 patients (64.71 %) had no depressive symptoms, 7 patients (20.59 %) had mild to moderate depressive symptoms, and 5 patients (14.71 %) had clinically relevant depressive symptoms. On the STAI-T, on average 42.38 points (*SD* = 12.35; range from 25 to 73) were recorded. Fifteen patients (44.12%) had “no or low anxiety”, 6 patients (17.65 %) had “moderate anxiety”, and 13 patients (38.24 %) had “high anxiety”. For the PSQI, a mean score of 6.94 (*SD* = 3.21; range from 2 to 14) was noted. Fourteen patients (41.18 %) were “good sleepers” while 20 patients (58.82 %) were “poor sleepers”.

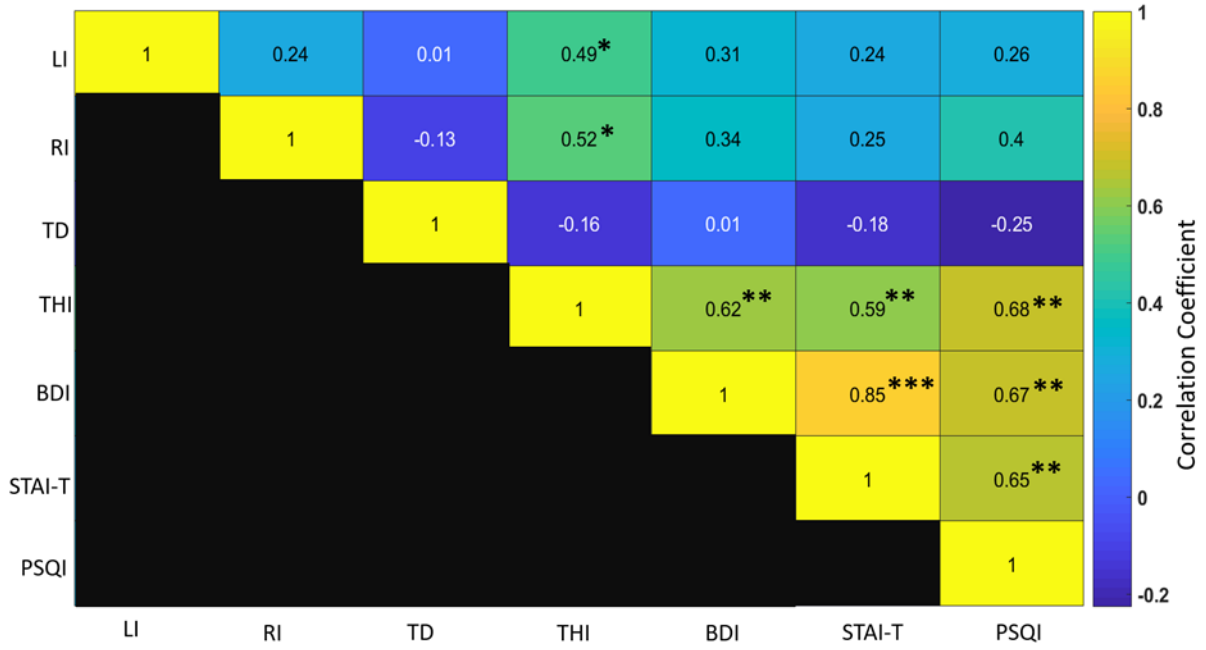
Intercorrelations between Tinnitus and Behavioural Measures

The intercorrelations between the behavioural questionnaires (THI, BDI, STAI-T, and PSQI) were all highly significant (all $p < .001$) with moderate to strong

correlations (.63–.85). They are presented in Figure 5. Gender, age, and education did not correlate significantly with any of the behavioural measures.

Figure 5

Intercorrelations between Tinnitus Severity and Behavioural Measures



Note. LI = Left intensity; RI = Right intensity; TD = Tinnitus duration; THI = Tinnitus Handicap Inventory; BDI = Beck Depression Inventory; STAI-T = State and Trait Anxiety Inventory – Trait; PSQI = Pittsburgh Sleep Quality Index.

*p < .05; **p < .01; ***p < .001

Severe versus Less-Severe Tinnitus Patients

EEG spectral analysis. A comparison between the absolute power (uV^2) during resting-state (1–48 Hz) of severe (n = 9) and non-severe tinnitus patients (n = 25) was calculated (Figure 6). Additionally, the absolute power was compared separately for the delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–24 Hz), and gamma (25–45 Hz) band (Figure 7). All values were corrected for multiple

comparisons. Significant differences were detected in the theta band (p = .013) with a higher power in the severe group. No significant differences in the absolute power were found for the delta (p = .324), alpha (p = .202), beta (p = .383), and gamma band (p = .555).

Figure 6

Comparison of Absolute Power Spectra in the Resting-State (1–48 Hz) between Severe (THI > 56) and Non-Severe Tinnitus Patients (THI ≤ 56)

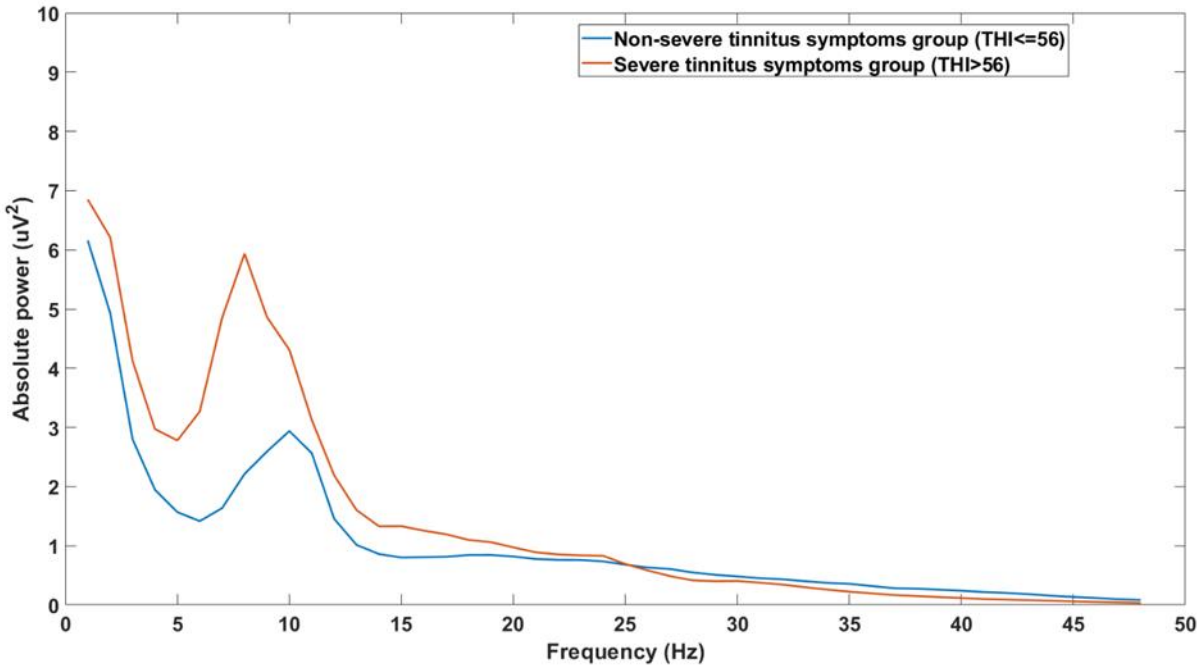
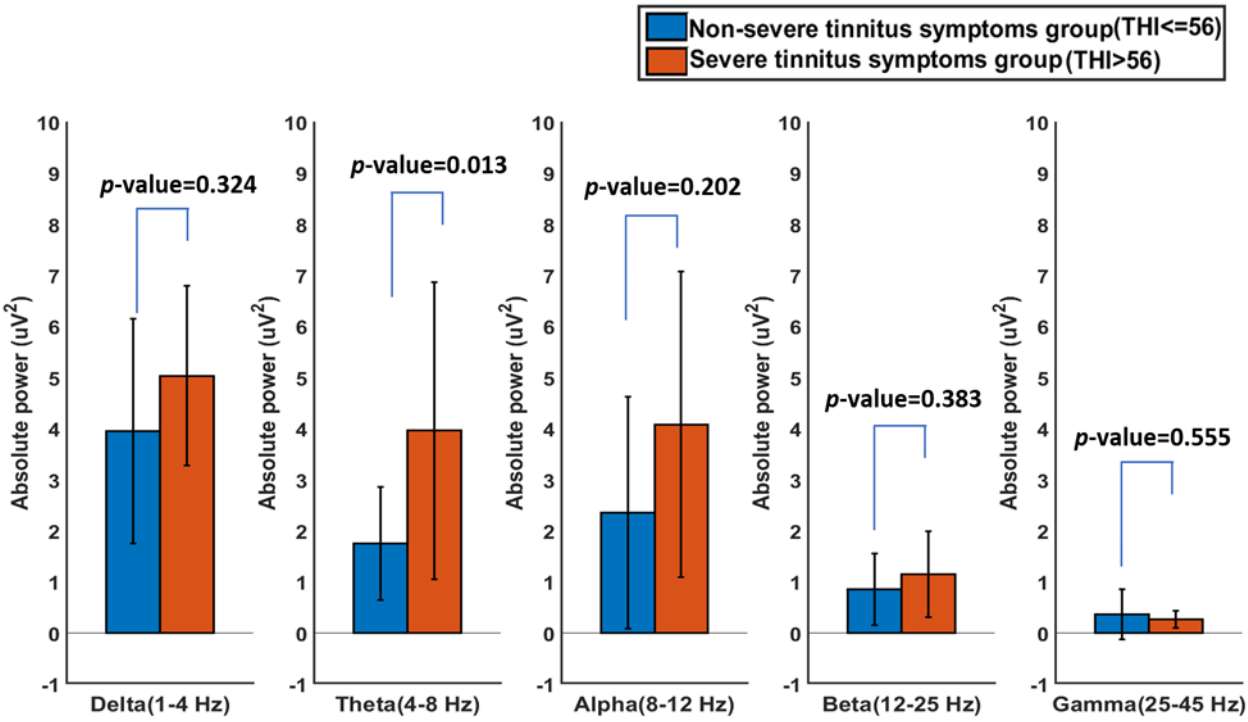


Figure 7

Absolute Power in the Five Frequency Bands Delta (1–4 Hz), Theta (4–8 Hz), Alpha (8–12 Hz), Beta (12–25 Hz), and Gamma (25–45 Hz) of Patients with Severe and Non-Severe Tinnitus

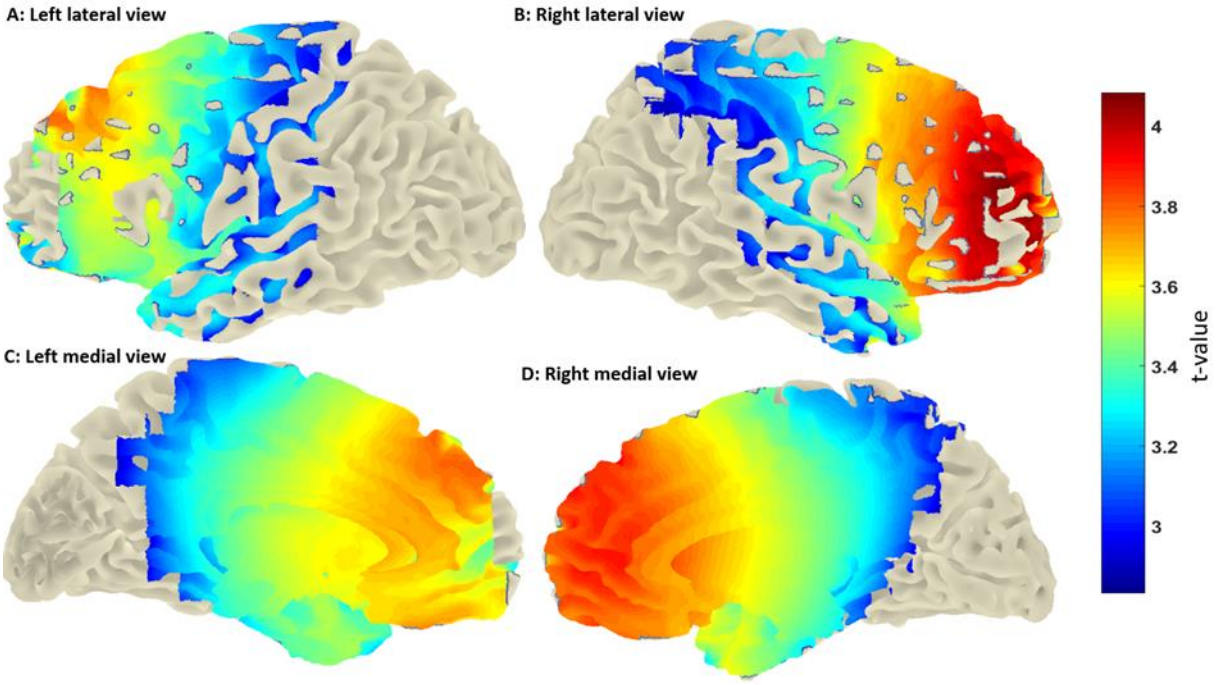


Note. Corrected *p*-values are shown on top of each subplot.

Source localization. The results of the sLORETA source localization method (Pascual-Marqui et al., 2002) in most of the frequency band parameters (delta, alpha, beta, and gamma) were similar in severe and non-severe handicapped tinnitus patients except for the theta band. The sLORETA current source density in the theta (4–8Hz) band was higher for severe handicapped patients than among non-severe handicapped patients in the dorsolateral prefrontal cortex (BA9), anterior prefrontal cortex (BA10), and middle frontal gyrus (BA46). The *t*-statistic values for significant voxels across the entire volume were mapped in Figure 8.

Figure 8

Brain Map of Significant Results for Current Density Amplitude Analysis in the Theta Band



Note. The sLORETA current source density in the theta band (4–8 Hz) was higher in patients with severe than non-severe tinnitus in the dorsolateral prefrontal cortex (BA9), anterior prefrontal cortex (BA10), and middle frontal gyrus (BA46). Displayed are: A) left lateral view on the cortical surface, B) right lateral view on the cortical surface, C) left medial view, and D) right medial view. Displayed is the sagittal plane (left and right hemispheres). The image shows significant results only.

Tinnitus Patients with Accompanying Depression or Anxiety

EEG spectral analysis. The 34 tinnitus patients were grouped according to their BDI and STAI-T results. Sixteen patients were assigned into the depression and/or anxiety group, and 18 into the no depression and/or anxiety group. The resting-state absolute power (uV^2) was compared (1–48 Hz) between the two groups (Figure 9). After correction, there were no significant differences in the absolute

power in the delta (p = .814), theta (p = .803), alpha (p = .803), beta (p = .814), and gamma band (p = .812).

Source localization. The sLORETA results did not show any significant difference between tinnitus patients with and without comorbid mood or anxiety disorders in the five frequency bands (delta, theta, alpha, beta, and gamma) which is shown in Figure 10.

Figure 9

Comparison of Absolute Power Spectra in the Resting-State (1–48 Hz) between Tinnitus Patients with and without Depression or Anxiety

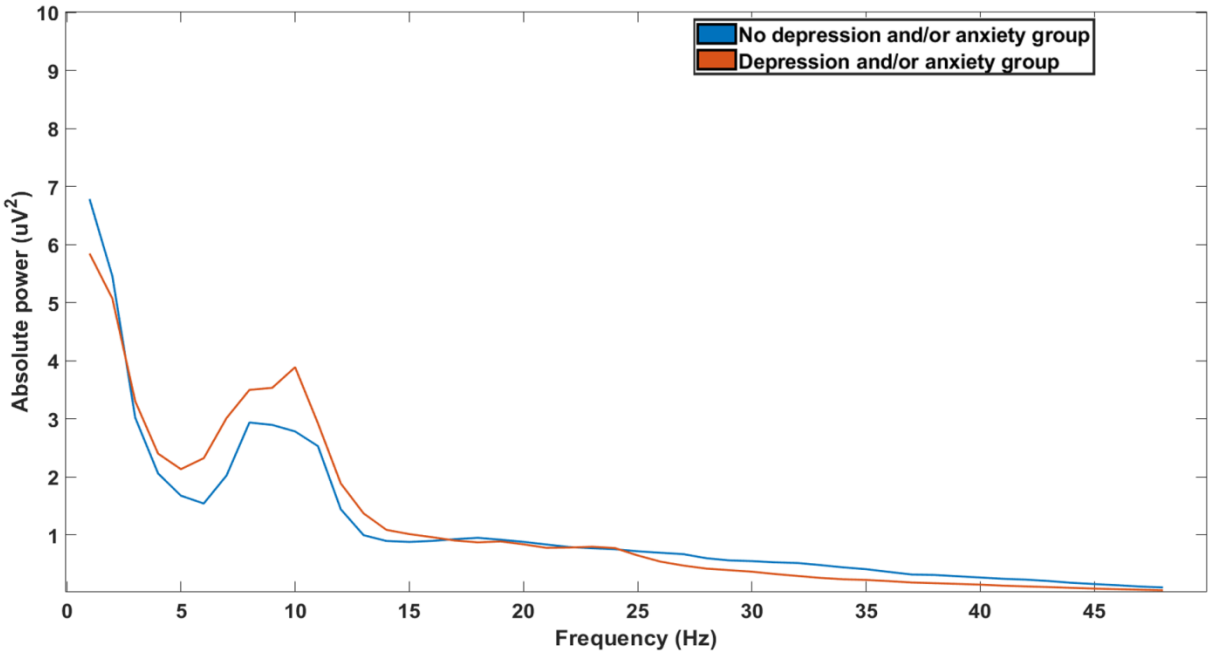
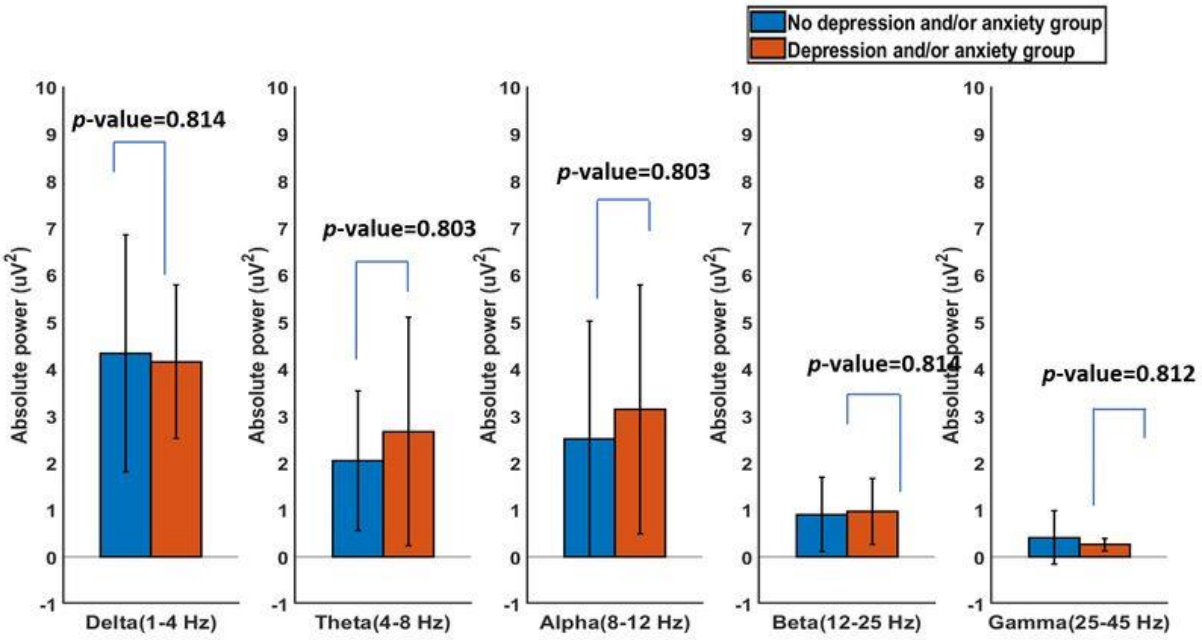


Figure 10

Absolute Power in the Five Frequency Bands Delta (1–4 Hz), Theta (4–8 Hz), Alpha (8–12 Hz), Beta (12–25 Hz), and Gamma (25–45 Hz) of Tinnitus Patients with and without Depression or Anxiety



Note. Corrected *p*-values are displayed on top of each subplot.

Discussion

The results suggest as expected a strong relation between different quality of life indices in tinnitus patients indicating that tinnitus patients severely affected by tinnitus additionally face accompanying psychological disorders such as depression, anxiety, and also sleeping difficulties. These findings are consistent with studies demonstrating the correlation between tinnitus severity and depression (Crocetti, Forti, Ambrosetti, & Del Bo, 2009; Folmer, Griest, Meikle, & Martin, 1999; Geocze, Mucci, Abranches, de Marco, & de Oliveira Penido, 2013; Robinson et al., 2003; Unterrainer, Greimel, Leibetseder, & Koller, 2003) tinnitus severity and anxiety (Andersson, Kaldo-Sandström, Ström, & Strömgren, 2003; Belli et al., 2008; Crocetti

et al., 2009), and tinnitus and sleep problems (Alster et al., 1993; Fioretti, Fusetti, & Eibenstein, 2013; Hallam, 1996). The strong correlation between depression and anxiety (Brown & Barley, 1992; Clark & Watson, 1991; Lovibond & Lovibond, 1995), depression and sleep problems (Alster et al., 1993; Alvaro, Roberts, & Harris, 2013; Nutt, Wilson, & Paterson, 2008), and anxiety and sleep problems (Alfano, Ginsburg, & Kingery, 2007; Alvaro et al., 2013; Gillin, 1998) also complies with previous research. Since the category of major depression does not include tinnitus as a characteristic entity, we are forced to conclude that depression, anxiety, and sleep disorders are rather a consequence of the helplessness induced by the uncontrollable phantom sound.

Regarding the different brain activation of patients severely affected by their tinnitus, compared to patients with mild or moderate symptoms, the frontal theta increase in the group with severe tinnitus can be seen as a sign for a frontal deviant function in severe tinnitus. This is in line with brain imaging studies showing that tinnitus patients have an altered activity in frontal regions (Araneda et al., 2018; Shulman et al., 2006; Shulman & Goldstein, 2002; Weisz et al., 2005a). However, this does not answer the question of the specific physiological nature of these dysfunctions.

The results can be interpreted in two mutually exclusive directions. On the one hand, if this prefrontal theta increase is interpreted as being an indicator of a lowered arousal, this would point towards an impaired top-down prefrontal cognitive executive control (“self-control”) of individuals with severe tinnitus, which would facilitate tinnitus generation and maintenance at auditory regions and block habituation mechanisms to the phantom tone (Araneda et al., 2018). This would imply that tinnitus patients have a trait-deficit or acquired deficit in executive functions compared to mild tinnitus patients. This was in fact shown in several studies using cognitive paradigms such as

the Go/no-go task (Araneda, De Volder, Deggouj, & Renier, 2015), the Stroop Test (Araneda et al., 2018; Stevens et al., 2007), and the Attention Network Test (Heeren et al., 2014). The results remained intact even if measures of hearing level, depression, and anxiety were regressed out by covariate analyses. The proposal of frontal theta as a sign of an impaired top-down function in tinnitus patients is also in accordance with an Attention-Deficit Hyperactivity Disorder (ADHD) study, according to which, resting-state frontal theta power correlates negatively with attentive information processing performance (Hermens et al., 2005). Training suppression of frontal theta as well as strengthening higher frequencies, mainly beta, with neurofeedback in ADHD correlates with improved attentional performance (Landes et al., 2017).

On the other hand, if a higher amount of frontal theta is interpreted as an indicator of increased attentional processing (Bruneau, Roux, Guérin, Garreau, & Lelord, 1993; Gevins, Smith, McEvoy, & Yu, 1997; Mizuki, Tanaka, Isozaki, Nishijima, & Inanaga, 1980), probably originating or correlating with hippocampal theta, it could indicate, that individuals with severe tinnitus focus their attention more to the tinnitus than less affected individuals with tinnitus. This hypothesis is supported by studies indicating that frontal theta activity increases during concentrated performance of mental tasks (Asada, Fukuda, Tsunoda, Yamaguchi, & Tonoike, 1999; Ishii et al., 1999) and with the memory load in working memory tasks (Jensen & Tesche, 2002), consistent with its hippocampal origin.

This interpretation, however, would ask for an explanation for the obvious lack of self- regulation capacity in the severe patients for the phantom-tone perceptions: with increasing attentional focus usually self-regulation results improve. We thus tend to favour the explanation of the theta increase as reflecting a mechanism of weakened inhibition of overexcitation in the primary and/or secondary auditory

system. Increasing (prefrontal) inhibitory potential by training increased alpha activity, as reported in some studies (Weisz et al., 2007a; Weisz, Hartmann, Müller, Lorenz & Obleser, 2011), indirectly supports such an interpretation because alpha is clearly related to increased thalamocortical inhibition at the cellular level (Andersen & Andersson, 1968; Steriade, 2006).

Summarized, we favour a tinnitus model that integrates our finding of an overactive prefrontal cortex with the current knowledge on tinnitus: Damage to the hearing system in association with ongoing distress is responsible for reorganization processes in the auditory cortex triggered by alterations in the central auditory pathway and leads to tinnitus generation (Eggermont & Roberts, 2004; Jastreboff et al., 1994; Schlee, Hartmann, Langguth, & Weisz, 2009a). In a second step, abnormal coupling with other higher-order brain areas, such as the prefrontal cortex or the limbic system, underlies its conscious perception. It is proposed that both steps are required for the maintenance of the of the tinnitus percept.

Chapter Three: General Discussion

Implications of Neural Findings for Tinnitus Therapy

The importance of the prefrontal cortex for tinnitus generation and maintenance as found in our study has also been stressed by Jastreboff (1990), who proposed that the prefrontal cortex integrates sensory and emotional components of tinnitus. A reduction of regional cerebral blood flow (rCBF) in the prefrontal cortex was shown when the tinnitus was suppressed by lidocaine administration or the presentation of masking sounds (Mirz et al., 1999). Moreover, an additional stimulation of the prefrontal cortex with high-frequency rTMS applied on the temporal cortex was able to enhance the efficacy of low-frequency temporal rTMS tinnitus therapy (Kleinjung et al., 2008).

Presumably due to the known difficulties of EEG measurements to show activation in subcortical areas, we were not able to detect activation in temporal areas. Yet, together with convincing results about the plasticity of the primary auditory cortex in tinnitus manifestation (Mühlnickel et al., 1998; Shore et al., 2016; Weisz et al., 2005a), our results are able to support the model of a tinnitus-related global network according to which prefrontal areas are part of a network which exerts top-down influence on the auditory cortices (Schlee et al., 2009b). The magnitude of this influence is linked to the subjective strength of the tinnitus distress. These proposals are supported by suggestions, according to which auditory map reorganization, although unambiguously shown, is not enough to satisfyingly explain the emergence of tinnitus (Weisz, Wienbruch, Dohrmann, & Elbert, 2005b).

Moreover, even if some tinnitus therapies are able to affect tinnitus, currently no single treatment alone can affect the tinnitus symptomatology to such a magnitude that the majority of patients show strong and long-lasting improvement. Thus,

regarding the treatment of tinnitus it is implicated that therapies should focus on both reducing the hyperactivity in the auditory cortex and reducing the top-down influence of the tinnitus-related global network on the temporal cortex. The former can be accomplished through a reinforcement of alpha activity with neurofeedback (Malekshahi et al., 2020) or low frequency targeted to auditory systems and high frequency rTMS targeted to the self-regulation regions of the prefrontal cortex (Plewnia et al., 2007b), while the latter can presumably be achieved through cognitive therapy. In a comparative study using resting-state MEG, neurofeedback showed a significant influence on neural activity in the auditory cortex whereas no significant neural changes were observable for rTMS (Hartmann et al., 2014).

Probably, both processes cannot be achieved with one single approach alone. This agenda is also set by Jastreboff and his TRT (2007), an approach that combines counseling and sound therapy. Yet, the efficacy of TRT could often not exceed CBT (Delb et al., 2002; Zenner et al., 2015). The presumed reason is that sound therapy cannot bring enough added value to increase the capabilities of CBT. However, since research on TRT is considered to be poor (Phillips & McFerran, 2010), additional research is needed to reveal more details about efficacy and neural substrates of this treatment.

Tinnitus patients with severe symptomatology mostly report a sudden onset of the phantom perception and the inability to control it. Together with the lack of any consistent positive treatment effect regardless of the nature of treatment (medical or psychological) on tinnitus loudness and no longitudinal confirmation of premorbid lack of self-control ability in people with severe tinnitus, the pathophysiology of theta increase found here should be seen rather as a consequence and not a causative trait variable in the etiology of severe tinnitus.

Even if tinnitus severity, depression, and anxiety are highly correlated, but the neural alterations of tinnitus severity are not, our interpretation of depression, anxiety, and sleep disorder as a result and not as a causal factor is supported. In addition, frontal theta increases, as found here, have also been shown as an indicator of increased stress in tinnitus patients (Weisz et al., 2005a) and depressive symptomatology in major depressive disorder (MDD) patients (Fingelkurts et al., 2006). However, in depressive patients, an asymmetry is indicated according to which depression correlates with a relatively greater right frontal resting state activity and a relatively lower left frontal resting activity (Fingelkurts et al., 2006; Henriques & Davidson, 1990; 1991). It is proposed that this overactivation of the right frontal area represents the unsuccessful effort to surmount its functional insufficiency (Rotenberg, 2004). There are no signs of increased severe tinnitus symptomatology at the neural level in depression. The lack of correlation of psychopathology and theta increase or any other changes in the neurophysiological frequency spectra in our study supports the interpretation of a common neural basis of psychopathology and tinnitus.

With regard to the lateralization of neural substrates of tinnitus, the positions are more heterogenous: A MSI (Mühlnickel et al., 1998), two fMRI studies (Melcher, Sigalovsky, Guinan Jr., & Levine, 2000; Smits et al., 2004), and a PET study (Lockwood et al., 1998) emphasized the involvement of auditory pathways contralateral to the side of the tinnitus perception. Based on this assumption, TMS protocols also included the placement of the circular coil over the contralateral auditory cortex for tinnitus suppression with temporary effects only (De Ridder et al., 2005). Contrary to these conceptions, two fMRI studies (Folmer, Stevens, Martin, Honey, & Thraves, 2002; Smits et al., 2007) indicated that tinnitus patients show greater activity in the auditory cortex ipsilateral to the tinnitus side. A third position is represented by a PET study which noted a predominant left-sided focal

hypermetabolism irrespective of the side of the tinnitus (Arnold et al., 1996). As a consequence of this ambiguity, it can be presumed that more knowledge about tinnitus lateralization would further promote tinnitus therapy, particularly stimulation techniques.

Limitations

Our results could not support the hypothesis of an altered activation in the auditory cortex of tinnitus patients (Weisz et al., 2007a; Weisz et al., 2007b). Possible reasons could be either the deep location of the auditory cortex since it is known that the more far away a location is from the surface of the cerebral cortex, the more problematic it is to have reliable results by means of EEG in general and sLORETA (Pascual-Marqui et al., 2002) in particular. Another reason could be that the samples compared in our study were severe versus non-severe tinnitus patients, and not tinnitus patients versus controls not suffering tinnitus. It seems probable that neural differences between tinnitus patients and healthy controls should also be recognizable in severe tinnitus versus non-severe tinnitus patients, however this assumption is not compulsory.

A further limitation of our study was that we measured the tinnitus through self-report measures like the THI and did not include more objective measures as covariates in the analysis, such as tinnitus frequency or tinnitus loudness assessed by audiometric testing. Although the main interest of our study was the tinnitus handicap, which can just be assessed by self-reports due to the limited correlation between audiometric tinnitus characteristics and degree of suffering (Hazell et al., 1985; Rachman & Philips, 1980), a more comprehensive and more objective assessment of an individual's tinnitus would have been feasible with the inclusion of such measures. Furthermore, the amount of hearing loss was not integrated in our

analysis; perhaps this would have brought new insights into the neural correlates of tinnitus.

Another source of weakness in this study was the inconsistency in the size of the subgroups: a small subgroup size of 9 individuals with severe tinnitus symptoms compared to 25 individuals in the non-severe tinnitus group. In addition, it must be mentioned that the participants were predominantly male. Few studies have given occasion to assume sex differences in tinnitus susceptibility. One of the few that found small gender differences is the study by Seydel, Haupt, Olze, Szczepek, and Mazurek (2013). Yet, since most studies did not find sex differences (Meric, Gartner, Collet, & Chéry-Croze, 1998; Pinto, Sanchez, & Tomita, 2010), it can be assumed that this does not limit the external validity of our findings, even though it is possible.

Areas for Future Research

Our conclusion of a prefrontal theta increase in severely affected tinnitus patients awaits confirmation in larger clinical trials. Likewise, our idea of a combined therapy, for instance neurofeedback plus CBT in order to simultaneously target the hyperactivity in the auditory cortex and the self-regulation regions of the prefrontal cortex, could be a fruitful area for future research. Based on this attempt, the effects of a combined therapy on the neural substrates of tinnitus could be investigated as well. If such an integrated therapy approach would be able to target not only the relief of the disturbing tinnitus but also reverse the effect of the “dark side” of cortical plasticity at the same time, is a question still in need of further investigation. However, it could be that this evidence first requires further progress of the current brain-stimulation techniques.

The likelihood that the prominent brain-stimulation techniques in the future will be invasive is not certain, but can be assumed to be very probable. Nonetheless,

further research is warranted to further investigate these treatment modalities in order to better understand how they work and how the brain responds to neuromodulation with the aim of an on-going technical development (this need of a proceeding development not only applies to invasive stimulation methods like DBS and intracranial auditory cortex stimulation but also to CIs). Thus, a stimulation using more tailored parameters and a regimen adapted to the individual brain pattern, as well as the ability to target particular brain areas with adjusted intensity, will probably be feasible. A first effort towards a personalized tinnitus treatment was attempted in a latest exploratory study using internet crowdsensing (Simoes et al., 2019). The results suggest that tinnitus aspects based on demographic and clinical characteristics can predict the response to various tinnitus treatments and thus support the hypothesis that tinnitus heterogeneity affects the variability in treatment response. Even if the magnitude of this effect was limited, it reveals that a personalized optimal tinnitus therapy is feasible, particularly if similar approaches would additionally include tinnitus-related distress, psychological comorbidities, and combined treatments and would have resource to big data and machine learning.

An example of a study covering a machine learning approach in the context of the prediction of an individual's response to tinnitus therapy was demonstrated in a recent publication (Niemann et al., 2020b). The aim of the study was to develop machine learning models that use clinical and sociodemographic features assessed before a multimodal treatment including CBT, informal counseling, and physiotherapy to predict the success of the treatment (the reduction of tinnitus related distress). With an area under the curve (AUC) of .890, the results show that machine learning is able to identify key features prior to therapy in order to characterize their effectiveness afterwards. If similar approaches are applied to multiple treatments in future studies, it could one day very well be possible that individual persons are

assigned to certain treatments in order to increase the probability of success of the therapy.

In this context, the methods for robustly and objectively determining the severity of tinnitus should be enhanced to be able to better evaluate the efficacy of tinnitus therapies, and the methods for distinguishing between responders and non-responders of specific treatments should also be improved. However, to achieve this goal, apart from the technical side, more sophisticated insights into the neurophysiological processes that cause tinnitus and that are responsible for its maintenance are needed in the coming years since the multiple presumed neuropathological mechanisms involved account for the heterogeneity of tinnitus perception observed in the population. This knowledge in turn would also promote the prospects of success for non-invasive treatment approaches for tinnitus patients with a less severe entity.

Furthermore, newest findings indicate that male and female tinnitus patients may react differently to different treatment options (Niemann, Boecking, Brueggemann, Mazurek, & Spiliopoulou, 2020a; Van der Wal et al., 2020). In the study of Van der Wal et al. (2020), female subjects profited more extensively than males from high-definition tDCS and orofacial physiotherapy, whereas males benefited more from CBT and TRT. A further study showed that women benefited more than males from a multimodal treatment encompassing CBT, information counselling, auditory attention training, and physiotherapy related to tinnitus-related distress and depression scores (Niemann et al., 2020a). Together with the ongoing scientific argument about the presence (Han, Jeong, Park, & Kim, 2019; Seydel et al., 2013) or absence (Meric et al., 1998; Pinto et al., 2010) of sex differences in tinnitus, these findings warrant further research. However, if the assumption of sex differences in reaction to specific tinnitus treatments is confirmed in the future, then

perhaps not only aspects such as the individual brain pattern or the type of tinnitus, but also the patient’s sex will influence the tailored choice of therapy to facilitate the best possible treatment success.

Chapter Four: References and Appendices

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Appendix

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PAPER

Real-time monitoring and regulating auditory cortex alpha activity in patients with chronic tinnitus

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Azim Malekshahi[1,8,9], **Rahim Malekshahi**[1,8], **Manuel Czornik**[1], **Jürgen Dax**[2], **Stephan Wolpert**[3], **Herbert Bauer**[4], **Christoph Braun**[2,5,6] **and Niels Birbaumer**[1,7]

[1] Institute of Medical Psychology and Behavioral Neurobiology, University of Tübingen, Tübingen, Germany
[2] MEG-Center, University of Tübingen, Tübingen, Germany
[3] Department of Otolaryngology, University of Tübingen, Tübingen, Germany
[4] Department of Social, Cognitive and Affective Neuroscience, University of Vienna, Vienna, Austria
[5] CIMeC, Center for Mind/Brain Imaging, University of Trento, Rovereto, Italy
[6] Department of Psychology and Cognitive Science, University of Trento, Rovereto, Italy
[7] Wyss Center for Bio and Neuroengineering, Geneva, Switzerland
[8] These authors contributed equally.
[9] Author to whom any correspondence should be addressed.

E-mail: azim.malekshahi@student.uni-tuebingen.de

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Abstract

Objective. Low levels of alpha activity (8–13Hz) mirror a state of enhanced responsiveness, whereas high levels of alpha are a state of reduced responsiveness. Tinnitus is accompanied by reduction of alpha activity in the perisylvian regions compared to normal hearing controls. This reduction might be a key mechanism in the chain of reactions leading to tinnitus. We devised a novel spatial filter as an on-line source monitoring method, which can be used to control alpha activity in the primary auditory cortex. In addition, we designed an innovative experimental procedure to enable suppression of visual and somatosensory alpha, facilitating auditory alpha control during alpha neurofeedback. *Approach.* An amplitude-modulated auditory stimulation with 40 Hz modulation frequency and 1000 Hz carrier frequency specifically activates the primary auditory cortex. The topography of 40 Hz oscillation depicts the activity of the auditory cortices. We used this map as a spatial filter, which passes the activity originating from the auditory cortex. To suppress superposition of auditory alpha by somatosensory and visual alpha, we used a continuous tactile jaw-stimulation and visual stimulation protocol to suppress somatosensory alpha of regions adjacent to the auditory cortex and visual alpha for local regulation of auditory alpha activity only. *Main results.* This novel spatial filter for online detection of auditory alpha activity and the usage of multi-sensory stimulation facilitate the appearance of alpha activity from the auditory cortex at the sensor level. *Significance.* The proposed procedure can be used in an EEG-neurofeedback-treatment approach allowing online auditory alpha self-regulation training in patients with chronic tinnitus.

1. Introduction

Tinnitus, the perception of sound without an actual external source, is the consequence of multiple factors rather than of a single disease entity [1, 2]. Due to the complexity and heterogeneity of tinnitus, it is difficult to develop a single effective treatment. Various treatment and management options have been proposed, but outcomes are variable and no generally accepted cure is available yet [3]. It has been observed that markedly reduced alpha activity (8–13 Hz) and increased delta (1–4 Hz) power in the auditory cortex and adjacent regions characterize tinnitus patients in comparison to normal hearing controls [4]. The differences were most pronounced in the perisylvian regions and were significantly correlated to tinnitus-related distress. It has been reasoned convincingly that alpha activity in the auditory cortex indicates the

same functional state as in other sensory structures [4, 5]. Since alpha activity in sensory cortices is a known indicator of ongoing inhibition and secures the balance of excitation and inhibition in sensory cortices [5, 6], reduced auditory cortex alpha activity might be a central key feature in the chain of reactions that leads to tinnitus.

In order to learn to permanently increase local alpha activity, and hence the inhibitory potential, a neurofeedback learning procedure is a promising non-invasive strategy. A large body of literature has demonstrated the ability of patients and healthy people to voluntarily regulate neuroelectric and neurometabolic brain activity [7, 8]. While the behavioral and therapeutic effects of neurofeedback show mixed results, evidence of symptom relief exists for some severe clinical disorders such as drug-resistant epilepsy [9], attention deficit disorder [10], chronic stroke [11], and Idiopathic Scoliosis [12]. Neurofeedback therapy in chronic tinnitus has been utilized in several small-scale exploratory studies. While the training of alpha increase in tinnitus has shown promising results [13–16], training of blood oxygenation level-dependent (BOLD) imaging in the auditory cortex using real-time functional magnetic resonance neurofeedback showed voluntary control of this metabolic phenomenon but negligible changes in perception [17].

The unspecificity of the target variable may constitute one of the major obstacles for consistent perceptual changes following alpha increase neurofeedback training. This is because the human waking EEG is dominated by alpha activity from the posterior visual system and, in states of motor quiescence, by the sensorimotor alpha rhythm. The sensorimotor alpha originates in the fronto-central areas and 'overrides' the alpha from the auditory cortex which projects mainly from a tangentially oriented temporal dipole to central areas at the midline. A successful neurofeedback training procedure therefore requires specific control of alpha activity from the auditory cortex with simultaneous suppression of the visual and somatosensory alpha activity. This is precisely what is realized in the presented training system.

The design of an auditory neurofeedback training system faces two problems. The first is how to derive EEG alpha oscillations in an online paradigm from the auditory cortex. Using EEG recording data from even high-density EEG does not automatically ensure that ongoing oscillatory activity from the auditory cortex can be recorded or trained. This problem originates from the general phenomena of volume conduction. Volume conduction is the cause for the dissipation of the electrical brain activity to sensors at different positions. In other words, the recording EEG electrodes are not in direct contact with the neurons; there are different tissue layers including cortico-spinal fluid, skull and scalp separating the two and smearing the local activity of a neural generator on the head surface [18]. The volume conduction effect leads to mixed activity of several simultaneously active sources recorded at individual sensors with EEG. This effect can lead to unreliable interpretations of the recorded EEG signal due to an unknown number of different, distant, neural sources [19, 20]. To reconstruct the sources from the recorded EEG data, which is referred to as 'inverse problem', a number of methods have been proposed with which the location of the sources of the EEG can be computed from measurements at the scalp. The inverse problem in the EEG is known as an ill-posed problem [21], because for all output voltages, the solution is non-unique [22]. This non-uniqueness might be somewhat ameliorated by introducing constraints and making assumptions that may be incomplete. The more physiologically appropriate these assumptions are, the more reliable are the source estimations [23]. Many techniques have been developed to overcome the inverse problem, allowing a spatial resolution of centimeters on the scalp compared to a millimeter scale on the cortex [19, 23, 24]. Some of the existing methods for solving the EEG inverse problem are beamforming methods such as dynamic imaging of coherent sources [25], source space-based distributed and sparse methods (sLoreta) [26]. Using the aforementioned source localization methods in real-time procedures for EEG neurofeedback of auditory cortex, allows to give a patient feedback directly from the ongoing activity in auditory sources. There are, however, three main issues with regard to the usage of these techniques in online procedures: the low signal-to-noise ratio (SNR), the limited time available for computations and the computation cost. We therefore propose a new method that does not encounter these three limitations. The second problem is auditory cortex alpha overlapping with alpha from neighboring sensory cortices, particularly visual and somatosensory/motor structures. The contribution of non-auditory alpha, in particular alpha originating from occipital cortex to the standard alpha neurofeedback procedure, is therefore important.

To overcome these two problems, we propose a novel method and a new experimental design for EEG auditory alpha neurofeedback. The method proposed consists of extracting a pattern of EEG data from a recording during stimulation of the primary auditory cortex before alpha neurofeedback sessions for each patient separately. This pattern would then be compared in real-time with the ongoing alpha EEG oscillation while neurofeedback sessions resulting in an index of how similar these two, ongoing and stimulation-based patterns, are. The simulated-based brain pattern functions like a spatial filter and corrects for the volume conduction effect and can be used to reinforce alpha activity originating from the primary auditory cortex. Since this similarity-based spatial filter detects the activity of the auditory cortex on the EEG electrode level-and not on the source space- we need to specify the particular channels that reflect auditory cortex activity, where the feedback is provided to

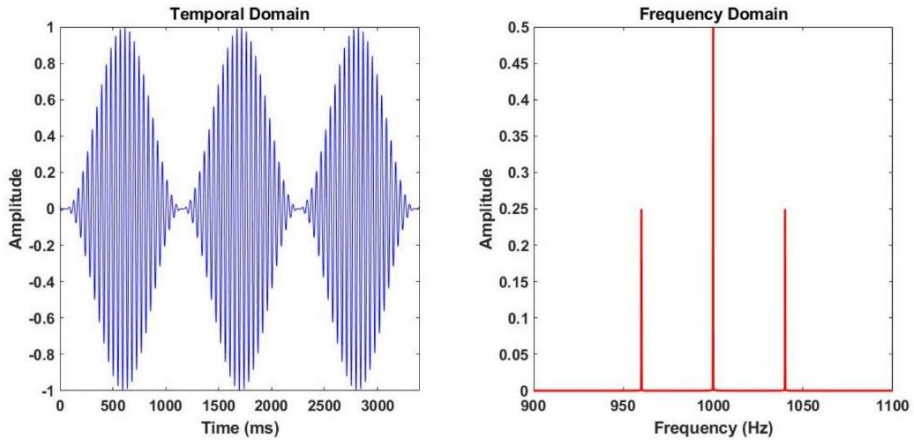

Figure 1. Amplitude modulated signal (time domain) and frequency domain. Its primary energy is at the carrier frequency (1000 Hz) and two sidebands of energy are located at the CF − MF (960 Hz) and CF+MF (1040 Hz).

the patient. In tinnitus EEG neurofeedback studies, fronto-central channels were generally selected due to the orientation of auditory sources [13]. However, the selection of the specific channels presumably projecting from the auditory cortex does not necessarily reflect the patient's auditory alpha if the volume conduction phenomenon is not considered. We propose a novel method for locating those specific EEG channels for neurofeedback. For this purpose, we have designed a localizer procedure with two aims; (1) to find the specific EEG channels for real-time feedback and (2) to design a spatial filter for each patient individually. Furthermore, the usage of multi-sensory stimulation might make it possible to suppress visual and somatosensory alpha during learning of alpha control. It is well documented that sensory input leads to modality-specific suppression of alpha activity at cortical regions involved in processing such inputs [27], thereby facilitating the appearance and recording of alpha activity from the auditory cortex.

2. Method

The similarity method consists of extracting a pattern of EEG data from a stimulation of the primary auditory cortex before neurofeedback sessions for each patient separately. This pattern will be compared in real-time with the ongoing alpha EEG oscillation during the neurofeedback sessions. The similarity method calculates online how much alpha oscillation from auditory cortex contributes to real-time neurofeedback recorded alpha rhythm at the electrode level. For this purpose, we employ localizer runs for two reasons; the first is to obtain an individual brain pattern when the primary auditory cortices are activated via specific auditory stimulation. Secondly, to specify the EEG channels (optimal channels) for which the auditory cortex activity contributes more to the recorded electrical activity than the other EEG channels. The feedback presented to the patient is a multiplication of alpha power in optimal channels with the similarity index, which is the final outcome of the similarity method (see below).

2.1. Eye movements calibration and localizer runs procedure

The actiCAP with its 64 active electrodes (based on high-quality Ag/AgCl electrodes) was placed with a standard EEG-cap using the Brain Products recording system (BrainAmp). Two reference electrodes were attached on both mastoids. In order to monitor vertical eye-movements, two electrodes were placed infra-orbital and supra-orbital to the right eye. One EEG electrode was placed 1cm lateral to the left outer canthus. The electrical activity of this electrode was then subtracted from the average of the other two infra-orbital and supra-orbital electrodes resulting in horizontal eye-movements activity. The eye movement calibration run consisted of two phases; a horizontal eye movement phase in which the patient had to look at the left and right part of the screen ten times (five times left and five times right), and a vertical eye movement phase in which the patient had to look at the upper and lower part of the screen ten times (five times up and five times down). The aim of eye movement calibration run is to specify a threshold for horizontal and vertical eye movements for online and offline rejection of EEG data.

We employed four localizer runs. Each of the runs 1, 2, 3, and 4 included 100 trials which lasted 1 s followed by 2 s of inter-trial interval. During a single run, patients were instructed to focus on a black cross in the center of a gray screen. In the first and third runs, *amplitude modulated auditory stimulation* was presented in each trial, with the patients' eyes open in the first run and closed in the third run. The auditory stimulus consisted of a sinusoidal carrier frequency (CF) of 1000 Hz and a Modulated Frequency (MF) at 40 Hz

(figure 1) presented through earphones. The modulation depth was set to 100% and the signal amplitude was set to prevent clipping during encoding. The sampling rate of the audio signal was set to 44.1 kHz. The intensity of the auditory stimulus was adjusted for each ear separately in accordance with the results of the audiometric test. Participants were permitted to blink every other trial after the offset of the auditory stimulation, which was cued by a 'green cross' (at the center of the screen on top of the black cross) for 2 s. In the second run, the patients were instructed to look at the black cross at the center of the screen while no auditory stimulation was presented. Again, blinking was allowed only when the green cross appeared. In the final run, they had to simply close their eyes upon the experimenter's cue.

As mentioned above, the aim of the localizer runs is to provide two kinds of information. They show us the brain pattern when the brain is stimulated with specific auditory stimulation and select those channels which reflect auditory cortex activity.

The analysis of localizer runs entails the following procedure: the EEG data was firstly re-referenced to the average of both mastoids. The mastoids were chosen as reference electrodes because, despite being close to all other electrodes, they receive less signals from the brain. In addition, since we anticipated that the main effects would be on the central channels due to the orientation of the sources of the primary auditory cortex, the EEG data were re-referenced to the mastoids channels to recapture the fronto-central activity. Horizontal and vertical eye movement signals in each trial (1 s) were calculated and each value in each time point of these signals was compared to the absolute maximum values (AMV) of eye movement calibration runs for both vertical and horizontal eye movements. If 0.3 portion of vertical or horizontal eye movement signal was larger than AMV, the trial was rejected.

Fourier transform with 1 Hz resolution was applied to determine the frequency in alpha (8–13 Hz) band in all localizer runs that had maximum power per Hz (frequency of maximum power (FMP)). Since the amplitude-modulated sound occurred in 40 Hz, the Fourier transform was applied to extract real and imaginary parts of 40 Hz as well as in FMP for each trial of each localizer run. To select optimal channels reflecting auditory cortex activity, we used singular value decomposition (SVD) in two steps.

Singular value decomposition produces a diagonal matrix s of the same dimension as X (m-by-n) of which the row of X are observations and columns of X are variables and s are non-negative diagonal elements in decreasing order, and unitary matrices u and v such that

$$[u, s, v] = svd(X) \tag{1}$$

$$X = u * s * v^T \tag{2}$$

$$U = u * s \tag{3}$$

$$P = s * v \tag{4}$$

The columns of u and the columns of v are called the left-singular vectors and the right-singular vectors of X, respectively, and s stands for singular values. P stands for pattern which, in our case, is the auditory steady state response (ASSR) pattern as brain response to the auditory stimulation or FMP pattern. U, can demonstrate which patterns can be selected as auditory and occipital patterns.

Firstly, for each trial of each localizer, we applied SVD on real and imaginary parts on FMP and 40 Hz separately to calculate two different topographies of the brain in each trial. The first column of u in equation (1) for 40 Hz is the topography of 40 Hz and the first column of u in equation (1) for FMP is the topography of FMP. The reason behind applying SVD on the trial data, and not the averaged data, is because the phase of FMP across trials is not constant. At this level, the observations are channels (61 EEG electrodes after excluding EOG electrodes) and variables are real and imaginary parts of 40 Hz or FMP. The object of this transformation is to gain both real and imaginary information simultaneously in one topography. Since we have four localizer runs, each consisting of 100 trials, as well as two topographies for each trial, in 40 Hz and in FMP, therefore we have a total of 800 topographies for all localizer runs. Secondly, we again applied SVD to these 800 topographies. At this level, the input for SVD is a matrix with 800 observations (rows) which represent the topography in 40 Hz and topography in FMP for all trials of localizer runs (1, 2, 3, and 4) respectively and variables (columns) are 61 EEG channels. Then U was calculated on the basis of equation (3).

The selection of channels for auditory and occipital areas was realized as follows:

1. As the number of trials for each localizer is 100, U is averaged in the first dimension with 100 row steps. This resulted in a new matrix called U_F with 8 rows and 61 columns which 8 rows corresponding to the FMP and the 40 Hz topography for each localizer run respectively. The columns are the components.
2. We plotted the cumulative sum of singular values (in descending order) with each value divided by the total sum of singular values prior to plotting. The plot will show the fraction of total variance retained versus the number of singular values. We preserved components which have around 98.8% or 99% of the total variance of the data.
3. In the component space (U_F), the component which reflects auditory activity has the larger absolute value in the first and fifths rows of U_F than in the second row and sixths rows of U_F respectively. Moreover it has the smaller absolute value in the third and seventh rows than in the fourth and eight rows in the

component space (U_F), respectively. The reason for this selection is the presentation of auditory stimulus in localizer run 1 and 3 where the ASSR has more weight than occipital alpha.
4. In the component space (U_F), the component that reflects occipital activity is exactly the reverse. This selection was chosen on account of the absence of the auditory stimulus in localizer 2 and 4 in which occipital alpha is dominant over 40 Hz brain activity.
5. Following selection of auditory and occipital components, we selected the singular values corresponding to that component and computed the pattern of ASSR and occipital alpha (equation (4)).
6. We plotted these two patterns.
7. The channels that reflect auditory activity are those with the highest values in auditory pattern and the lowest values in occipital pattern (minimal alpha).
8. The channels that reflect occipital activity are those channels with the maximum value in occipital pattern and the minimum value in an auditory pattern (maximal alpha).

2.2. Similarity method and online EEG signal processing

The amplitude-modulated auditory stimulation with 40 Hz modulation frequency and 1000 Hz carrier frequency activates the primary auditory cortex in particular [28, 29]. The topography of 40 Hz is a map of the brain activity that depicts the activity of the auditory cortices. This map can therefore be used to determine to what extent the brain activity in a specific time window resembles auditory cortex activity. We used this map as a spatial filter, which stresses the activity from the auditory areas. In real-time, the topography of each frequency in alpha band (8–13 with 1 Hz resolution) has to be compared to the topography of 40 Hz which results in a similarity index. On the one hand the similarity index reflects how active non-auditory alpha sources are. This means that an increase in the similarity index would be accompanied by less presence of non-auditory alpha sources, yet it does not reflect the amplitude of auditory sources. On the other hand, the alpha power from the optimal channels is a representation of the summation of the amplitude of alpha sources. Therefore, the product of similarity index and alpha power of the optimal channels indicats how much alpha auditory source is contributing to the alpha power on the electrode level.

We selected 1 Hz resolution for less computational time in online processing. The segment of data for real-time analysis was 1 s and the overlap of the window between two segments was 500 ms. The real-time calculation for each segment of data (1 s) followed these steps:

1. Absolute maximum values of the horizontal and vertical eye movements for online rejection were extracted from the eye calibration runs.
2. The 61 EEG channels (EOG channels excluded) were divided into left and right hemispheres. The midline EEG channels were assigned to both the left and right hemispheres to avoid any lateralization problems. This separation was proceeded because the auditory stimulus which we present to a patient in the localizer 1 activates the left and right auditory sources combined. Under this condition, the left and the right auditory sources are highly correlated [29–31]. Furthermore, the spontaneous alpha oscillations in left and right auditory cortices are not correlated. Thus, we calculated the real-time auditory EEG for each hemisphere separately, and the final output feedback consisted of the sum of the left and right hemispheres.
3. The imaginary and real parts of the Fourier Transformation at 40 Hz for 61 EEG channels were extracted from the first localizer run. We then applied SVD on the real and imaginary parts on the left and right hemispheres channels separately. The first column of u in equation (1) for the right hemisphere was the 40 Hz topography of this hemisphere. Likewise, the first column of u in equation (1) for the left hemisphere was the left hemisphere topography of 40 Hz.
4. Each segment of data (1 s) was examined to ascertain whether it contained EOG artifacts or not in the same manner as for the localizer runs. If recorded data did not contain EOG artifact, the calculation continued.
5. The cleaned segment of the data was decomposed with Fourier Transformation, giving real and imaginary parts for 8, 9, 10, 11, 12, and 13 Hz. We then applied SVD on real and imaginary parts of each frequency for the right and left hemispheres EEG channels respectively.
6. The similarity between the topography of each alpha frequency activity of the recorded data with the topography of the 40 Hz amplitude modulated signal is an index of the extent to which the alpha oscillation from non-auditory cortex sources are active. Due to the fact that these topographies are two non-zero vectors, we use the inner product which divulges of the one vector is pointing in the direction of the other one. The inner product, as a measure of similarity between these two non-zero vectors for two pairs, is calculated and the maximum value of each pair is selected as the similarity of

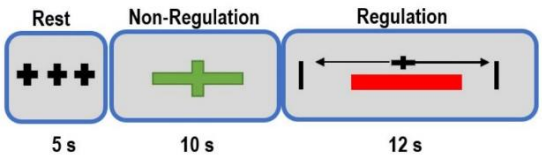

Figure 2. Experimental protocol. The patient receives 20 trials per run. Each run starts with 5 s rest (black cross on a gray background). It is followed by 10 s of non-regulation phase which is cued by a green fixation cross in the center. During this phase, pink noise is presented to the patient and he/she is allowed to blink or to move his/her head. Then, there is a 12 s regulation phase, cued by two black horizontal arrows. During this condition, a red horizontal thermometer will be extended/shortened from the center of the screen based on the amount of the alpha activity coming from the auditory cortex. In addition, during rest and regulation phases, a tactile stimulation consisting of airflow with constant velocity stimulates the mental protuberance.

right and the left hemispheres respectively for the specific frequency F (equations (5) and (6)).

$$\mathrm{SI_{RF}} = \max(\langle U_{\mathrm{RL}} \cdot U_{\mathrm{1RF}} \rangle, \langle U_{\mathrm{RL}} \cdot U_{\mathrm{2RF}} \rangle) \quad (5)$$

$$\mathrm{SI_{LF}} = \max(\langle U_{\mathrm{LL}} \cdot U_{\mathrm{1LF}} \rangle, \langle U_{\mathrm{LL}} \cdot U_{\mathrm{2LF}} \rangle). \quad (6)$$

U_{RL} and U_{LL} are the topographies in 40 Hz for the right and left hemispheres. U_{1RF} and U_{2RF} are the first and second columns of u in equation (1) for frequency F of the right hemisphere. U_{1LF} and U_{2LF} are the first and second columns of u in equation (1) for frequency F of the left hemisphere. $\mathrm{SI_{RF}}$ and $\mathrm{SI_{LF}}$ are the similarity indices for the right and left hemispheres for frequency F respectively. The dot $\langle \cdot \rangle$ is the inner product.

7. The optimal EEG channels were also divided into the left and right hemispheres. EEG midline channels were assigned to both the left and right hemispheres. The power for the EEG channels for the left and right hemisphere was calculated for each frequency in alpha band (8–13) with 1 Hz resolution. Then, it was multiplied by its own similarity index (equations (7) and (8)).

$$\mathrm{FP_{LF}} = \mathrm{Power_{LF}} \times \mathrm{SI_{LF}} \quad (7)$$

$$\mathrm{FP_{RF}} = \mathrm{Power_{RF}} \times \mathrm{SI_{RF}}. \quad (8)$$

$\mathrm{Power_{RF}}$ and $\mathrm{Power_{LF}}$ are the power in frequency F for the right and left optimal channels. $\mathrm{FP_{RF}}$ and $\mathrm{FP_{LF}}$ are the filtered power in frequency F for the right and left optimal channels.

8. Since the frequency resolution is 1 Hz, we had six filtered powers for left hemisphere and six filtered powers for the right hemisphere. The total filtered power for both left and right hemispheres could therefore be calculated (equation (9)).

$$\mathrm{TFP} = \sum_{F=8}^{F=13} \mathrm{FP_{LF}} + \sum_{F=8}^{F=13} \mathrm{FP_{RF}}. \quad (9)$$

TFP is the total filtered power for one segment of data (1 s) for alpha band (8–13 Hz) with 1 Hz resolution. F is a frequency in alpha band from 8 to 13 Hz.

3. Experimental procedure

Prior to the actual neurofeedback training, all patients participated in 3 experimental visits, each lasting for approximately 2 h, including preparation. The number and locations of the EEG channels were identical to those in the localizer runs. Each run, composed of 20 trials, began with a 5 s rest period (black cross on a gray background), followed by a 10 s non-regulation phase, which was cued by a green fixation cross in the center of the screen. There were two reasons for implementing the non-regulation phase. Firstly, it gave time the patient to blink or move the head if necessary. Secondly, in the 'non-regulation' phase the patient was presented with the specific auditory stimulus (pink noise) which gives the patient a relief of tinnitus through masking the tinnitus during non-regulation phase [32]. It also suppresses the alpha oscillation in the auditory cortex during its presentation, which could lead to a rebound of alpha oscillation in the regulation phase. This rebound can exceed the prestimulus baseline level of alpha oscillation [33] facilitating alpha upregulation in the regulation phase.

The non-regulation phase was followed by 12 s of regulation, cued by a black horizontal arrow pointing in both opposite horizontal directions. A red horizontal 'thermometer' was extended/shortened from the center of the screen, depending on the amount of alpha activity from auditory cortex (figure 2). The segment of data for real-time analysis was 1 s and the overlap between two segments was 500 ms. The same similarity method was applied in the feedback training phase and the rest period. Online individual normalization during regulation phase for each segment of the data (1 s) was carried out such that the average of output indices (TFP) for rest periods (5 s) was calculated, regulation phase output index (TFP) for each segment of the data (1 s) was then subtracted from the averaged rest and, finally, also divided by the averaged rest value. This is the final total filtered power (FTFP) which the patient

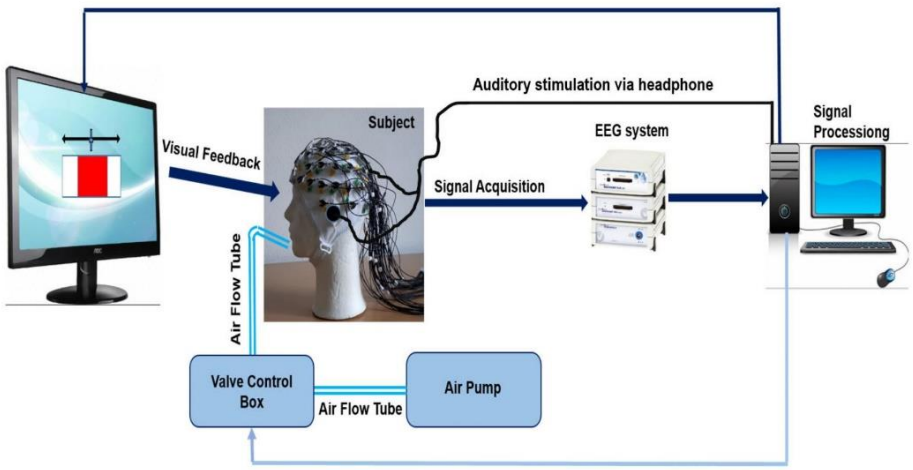

Figure 3. Experimental situation. Neurofeedback setup including EEG, an air-pump for the tactile stimulation of the mental protuberance, auditory stimulation via earphones and hardware for online EEG signal processing.

perceives as a red horizontal thermometer. During the 'non-regulation' phase, the patients are permitted to blink. However, if the patient blinks during the other intervals and the rejection criteria—which is the same as in localizer runs procedures—is met, the feedback value is not updated for that time interval. During the 'regulation' phase, participants were instructed to self-up-regulate the alpha activity. No specific instruction for eventual strategies was given. If patient asked, he/she was told 'to try his/her own strategy, everybody has his/her own strategy'. Additionally, during the rest and regulation phase, we presented a tactile stimulation which consisted of an air flow with constant velocity that stimulated the mental protuberance to block sensory motor alpha-rhythm (SMR). The stimulation of the mental protuberance suppresses the alpha activity in somatosensory regions adjacent to the auditory cortex. We hypothesize that suppression of somatosensory alpha through tactile stimulation and suppression of occipital visual alpha from the visual stimulation of the visual feedback signal at the screen facilitates auditory alpha self-regulation. The neurofeedback setup is shown in figure 3, which includes EEG, auditory stimulation via earphones, tactile stimulation and online signal processing hardware.

4. Results

Using simulated data to recognize alpha sources originating from non-auditory and auditory brain regions, we will first demonstrate the efficiency and validity of the similarity method. We will then proceed to demonstrate the method of identification of auditory cortex sources in the alpha band of spontaneous cortical rhythms in 3 tinnitus patients during the neurofeedback paradigm.

4.1. Simulated data

We simulated sources in the alpha rhythm using FiledTrip Toolbox [34] in different locations inside a regular grid. The aim was to ascertain how the similarity method recognizes that the sources do not originate from primary auditory cortices. This was determined by the extent to which the pattern of each source resembles the pattern of 40 Hz sources as representative of ASSR. We used an analytical concentric sphere model with 3 spheres [35] for forward calculation. There are two sequences of simulations:

1. Having defined a head model, the grid points of a regular grid inside the 3 spheres with 1 cm resolution are selected. Based on this resolution there are some dipoles inside and outside the spheres. The position of those dipoles which are located inside the spheres are selected for reconstruction of electrode-level EEG data. There are two main pair sources, the first pair, 40 Hz frequency sources on both primary auditory cortices and the other 10 Hz frequency sources in left and right primary auditory cortices representing auditory alpha. The momentum of the left 10 and 40 Hz sources is the same and also the momentum of the right 10 and 40 Hz sources is the same. The other remaining 10 Hz sinusoidal sources are located in non-primary auditory regions to simulate spontaneous alpha oscillatory brain activity outside primary auditory cortices. Firstly, the forward model is calculated for both left and right 40 Hz sources and then in the same location, the forward model for two 10 Hz sources is computed. Then, the forward models are computed for

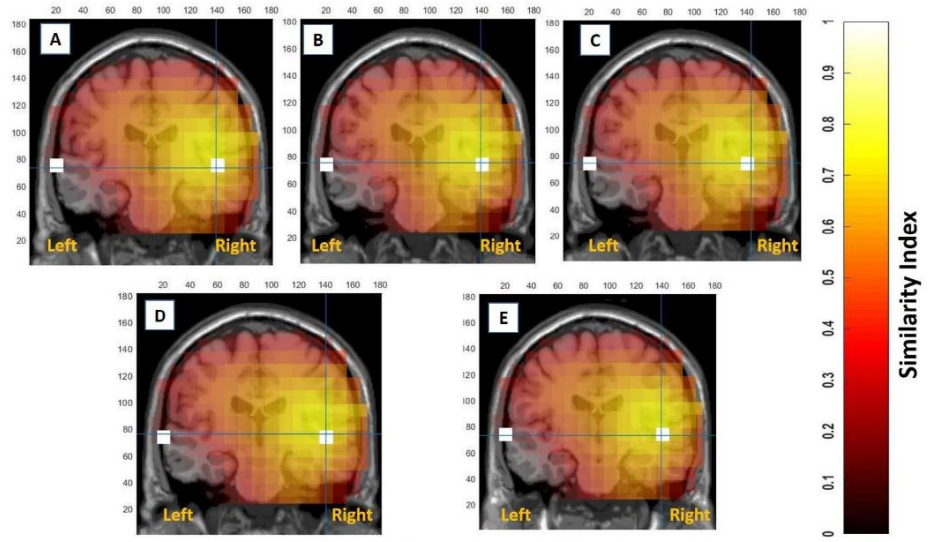

Figure 4. Result of the similarity index calculations for the first simulated data sets (A)–(E). In all data sets, the similarity indices have the highest value in the auditory cortex. The result shows that the closer the sources are to the auditory cortex, the higher are the values for similarity indices. Since the momentum of all non-auditory cortices in this data sets is the same as in the right auditory cortex, the high simliartiy values are mostly located on regions adjacent to the right auditory cortex. In the first dataset (A), the phase difference bewteen auditory and non auditory sources are zero. In the second dataset (B), the phase difference is 45°, in the third dataset (C) the phase difference is 90°, in the fourth dataset (D), the phase difference is 135°, and in the fifth dataset (E), the phase difference is 180°.

all remaining sources with different locations compared to the two main pair sources. As each source can have a different phase and momentum, the number of forward models for each source with a specific location is unlimited. Although it is impossible to compute all forward models for all combinations of phase differences between primary auditory and non-primary auditory sources, we cover some possible cases to check the efficiency of this method in distinguishing between primary auditory and non-primary auditory alpha sources. After the calculation of all forward models for all sources, the similarity method is applied to each forward model to investigate to what extent the brain pattern from each source activity resembles the pattern from ASSR-simulated sources. For the two 10 Hz sources, their similarity indices are displayed in the left and right source positions (figure 4).

For all other sources, the average of the left and right hemispheres' similarity indices is displayed in source locations (figure 4). Five sets of data are stimulated. In the first data set (A), all non-auditory sources have the same phase as the right 40 Hz source and all their momentums are the same as the right 40 Hz source. In the other four remaining datasets (B)–(E) all non-auditory sources have 45, 90, 135, and 180° phase difference with the sources located in the primary auditory cortex but their momentums are the same as the right 40 Hz sources. The result of the five simulated data sets is shown (figures 4(A)–(E)).

2. The ASSR forward model is based on both the left and right 40 Hz sources, which highly correlate [30], leading to the phase difference between them being very small. Therefore, there is only one topography for the two 40 Hz sources. However, the scenario for the left and right 10 Hz sources is different, because there might be a phase difference between the two, which in turn leads to different topographies. Hence, one simulation of data from only the two 40 Hz sources with zero phase difference is calculated, but the phase difference between two 10 Hz sources begins with 0° and gradually increases in 10° steps until the difference reaches 180°. The forward model is first calculated for the two 40 Hz sources, and then in each step, the forward model is calculated for the two 10 Hz sources, followed by the similarity method which compares the patterns of two 40 Hz and two 10 Hz. The result is presented in the colormap representation (figure 5).

4.2. Physiological data

Three male patients with chronic tinnitus (mean age: 48 ± 8.1 years) were recruited for this phase of the study. All three patients provided written informed consent after receiving a detailed explanation of

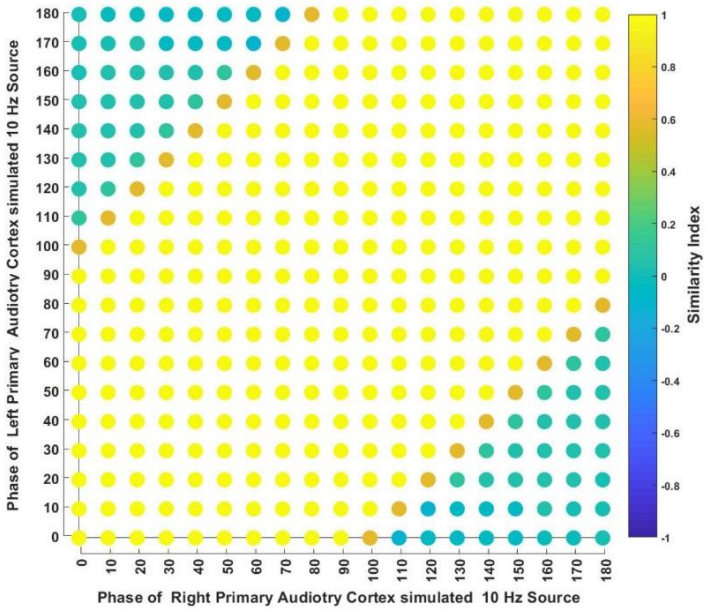

Figure 5. Result of the similarity method regarding the phase difference between two auditory 10 Hz sources. The resolution is $+10°$. The x-axis is the phase of the right primary auditory cortex simulated 10 Hz and the y-axis is the same for the left primary auditory cortex. The color bar on the right side indicates the mapping of similarity indices in the color map. The similarity indices are negative in the top left and the right bottom of the figure.

the experimental procedures. The study is in full compliance with the ethical practice of Medical Faculty of the University of Tubingen. Informed consent approved by Internal Review Board of the Medical Faculty of the University of Tubingen is in accordance with the research protocol, following the principles as laid down in the current version of the Declaration of Helsinki.

4.2.1. Localizer runs.

The result of the localizer runs specifies those channels that reflect auditory cortex activity. The occipital and visual patterns and the difference between these two patterns for these three patients are depicted (figure 6). Each pattern consists of an array which assigns a negative or positive value to each channel. Only the absolute value of each element in each array shows how much that channel reflects activity in that pattern. Therefore, we used the absolute value of each pattern. Auditory pattern reflects its own activity in central and frontal regions, visual pattern reflects its own activity in the occipital and frontal regions. The difference of these two patterns is the result of the subtraction of these two patterns, which cancels out those regions in which both patterns show high activity (the frontal region). The optimal channels selected in these patients are consistent with those channels selected in other EEG neurofeedback studies for tinnitus patients [13, 14]. A further consistency with other auditory studies, in particular with steady state response sources analyses is that selected channels are in those regions of the brain towards which auditory cortex dipoles are oriented [36, 37]. Table 1 shows the optimal EEG channels for the three patients. Variability of the visual and auditory patterns across these three patients is shown (figure 7).

4.2.2. Similarity method with physiological data.

We postulated that the similarity method could reflect the auditory cortex activity without using any standard source localization methods. The total filtered power (TFP)for one segment of data (1 s) for alpha band (8–13 Hz) with 1 Hz resolution was calculated using equations of the section 2.2 (the Similarity method and online EEG signal processing). All TFP values for all three visits were sorted from minimum to maximum and divided into 30 bins where each bin corresponds to a specific range of TFP. Then all the segment data (1 s) which corresponds to each bin were extracted from the regulation phase data. Source localization for all the MNI (Montreal Neurological Institute) atlas cortical regions were then performed for all segments in each bin and for each frequency in alpha band. The regions of interests were right temporal, left temporal, right auditory cortex, left auditory cortex and the regions of non-interest were right frontal lobe, left frontal lobe, right occipital lobe, left occipital lobe, right paracentral-central, left paracentral-central, right parietal and left parietal. We calculated the volume conduction model of the template MRI of Fieldtrip data set on the basis of boundary element method (BEM) [38]. We then used one of the beamforming source localization methods, dynamic imaging of

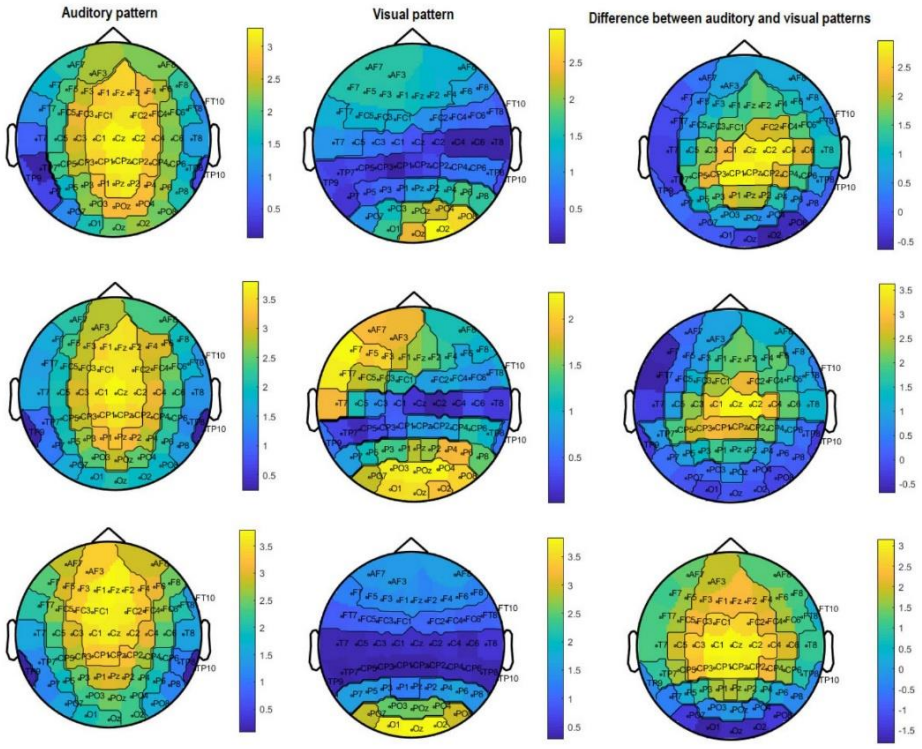

Figure 6. Topography decomposition for the most relevant channels reflecting auditory and occipital activity. Each row corresponds to one patient. The first and second columns show the auditory and occipital patterns for three patients. Each pattern consists of an array which assigns a negative or positive value to each channel. Only the absolute value of each element in each array shows how much that channel is reflecting activity in that pattern. Therefore, we used the absolute value of each pattern. The difference of these two patterns which is the result of the subtraction of these two patterns (last column). In the third column auditory channels are those with high positive values in the fronto-central and centro-parietal regions, while the occipital channels are those with high negative values in the occipital region. The description of how the specific channels can be selected is included in the section 2.1.

Table 1. Channels mainly reflecting the activity from auditory cortex.

Patient	
1	FC2-FC4-C1-Cz-C2-C4-C6-CP1-CPz-CP2
2	FC1-FC2-C1-Cz-C2-C4-CP1-CPz-CP2
3	FC1-FC2-FC4-C3-C1-Cz-C2-C4-CP1-CPz-CP2

coherent sources (DICS) [25] to calculate the power of alpha band (8–13 Hz) with 1 Hz resolution at source level in the MNI cortical brain regions. To compare alpha power of one bin to the other in one cortical region, the alpha power in that region is divided to the sum of alpha power in all cortical regions. This allows the comparison of the relative alpha power across the bins. The results over the different frequencies in the alpha band were averaged and are displayed (figure 9). The distribution of the averaged SI_{RF} and SI_{LF} across all frequency F with 1 Hz resolution in the alpha band for each patient and across these three patients is shown (figure 8).

5. Discussion

Real-time source localization of EEG data is a challenging procedure. The low signal to noise ratio, the time-consuming procedures of the inverse solutions and the limited time points of the data make a real-time source localization difficult to apply in real-time EEG neurofeedback. We therefore implemented a novel similarity method which functions as a spatial filter to prevent alpha feedback from non-auditory cortices.

The effectiveness of this method has been established with both simulated and physiological EEG data. Figures 4(A)–(F) demonstrates that the similarity indexes are positive in the auditory cortices and the adjacent regions only. Although the adjacent regions to auditory cortex have high similarity indices, presenting tactile stimulation during actual EEG neurofeedback supposedly suppresses the alpha activity in these regions. Furthermore, the phase difference between non-auditory sources and both ASSR sources ranges

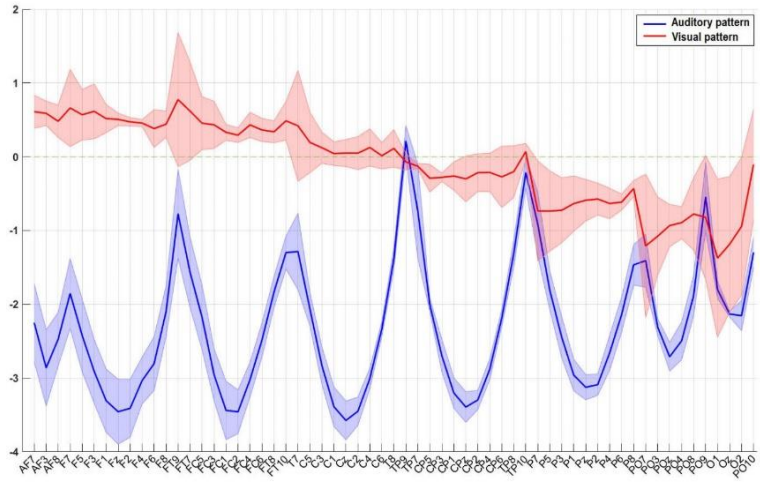

Figure 7. Topography decomposition for reflecting auditory and visual patterns across three patients. The red line depicts the occipital activity pattern (shadow is the standard deviation) and the blue line the auditory activity across three patients (shadow represents the standard deviation). The absolute values of y-axis reflect how much the component contains auditory or occipital activity (no unit).

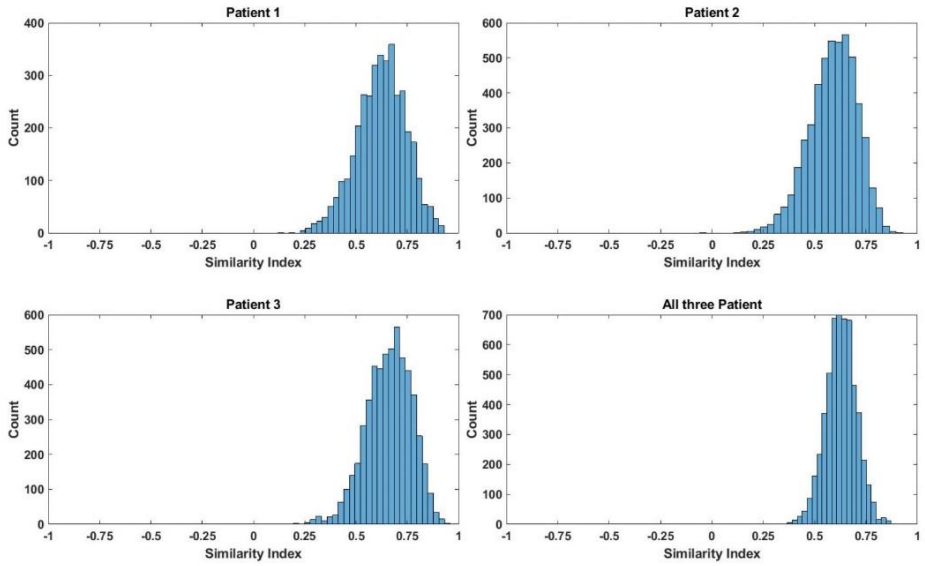

Figure 8. Histogram of averaged total similarity index (left and right hemispheres) for all frequencies in the alpha band (8–13 Hz) with 1 Hz resolution for each patient and the right lower plot is the histogram of total similarity index across three patients. The x-axis represents the similarity index and the y-axis is the count which corresponds to each bin.

from 0 to 180° in 45° steps, showing that the similarity method is also robust to phase differences. The other factor which should be considered is the phase difference between two 10 Hz sources in the auditory cortices. Since the phase difference between two 40 Hz sources as highly correlated sources is very small, which leads to having only one ASSR topography. Therefore, only one ASSR topography was compared with different alpha auditory topographies in the second phase of simulation. Figure 5 shows the effect of the phase differences among the two main 10 Hz sources. It can be seen that the similarity method tolerates phase differences between the two 10 Hz sources approximately up to 100°.

Since the similarity method recognizes the auditory activity at the sensor level, the channels from which the alpha feedback is passed on to the patient must be specified. Table 1 shows the optimal channels for these three patients which are in the centro-parietal, central, and fronto-central region. Figure 6 dem-

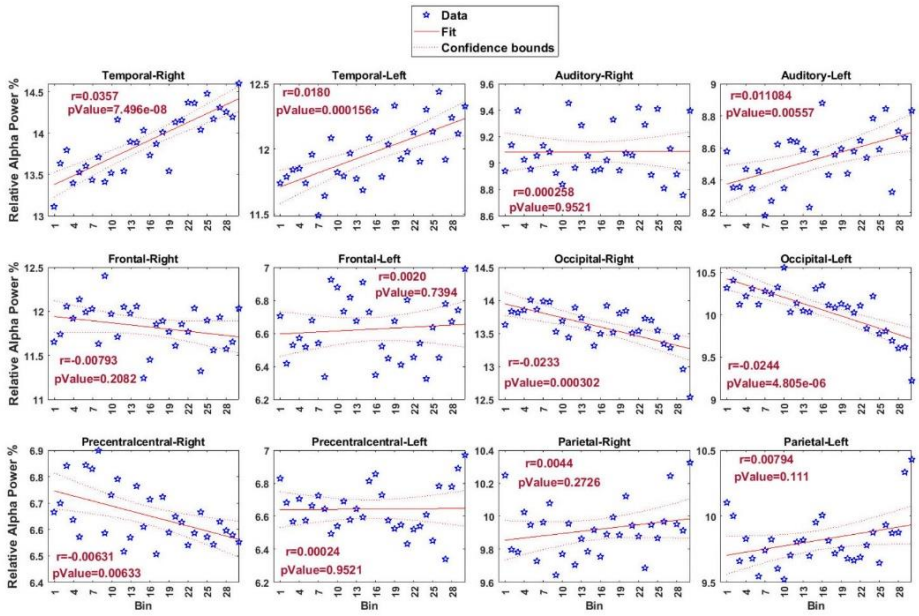

Figure 9. Relative alpha power of each cortical brain region (based on the MNI atlas coordinates). Relative alpha power is the alpha power of each cortical region in each bin (a TFP range) divided by the sum of alpha power in all cortical regions in the same bin (details in section 4.2.2). The *x*-axis displays up to 30 bins. Each bin corresponds to a specific TFP range (corresponding to 158 segments, 1 s each) of the alpha-regulation phase data. The *y*-axis shows the percentage of relative alpha power of a specific brain region. The corrected p-values using the Benjamini and Hochberg method [39] for each region and the slope of the fitted line are shown in each subpanel. The regions of interests are right temporal, left temporal, right auditory and left auditory.

onstrates auditory and visual patterns. The auditory pattern manifests its activity neighboring the midline electrode from parietal to the frontal areas, while the visual pattern displays its activity in occipital and frontal regions. The difference between these patterns shows high positive values in the central area and high negative values at the occipital areas (the last column of figure 6). This in turn determines the optimal and occipital channels respectively.

Each training session lasted 2 h including preparation and required focused attention. We reduced this amount of time to a maximum of 1 h for the second phase of the study by reducing the number of EEG channels, which might influence the accuracy of the similarity method. Hence, following the selection of optimal channels, a number of channels reflecting occipital activity were also selected to compare -to some extent- the whole topography of brain activity during real-time neurofeedback with the ASSR topography acquired during the first visit (localizer run 1).

It should be emphasized that with this small number of participants we cannot statistically test the variability across these patients. But as these tinnitus patients have been recruited based on the specific inclusion criteria, like a Tinnitus Handicap Inventory (THI) above 48, the variability across them, is very small. From figures 6–8 could be seen that the manifestation of auditory and visual patterns, the optimal channel locations and the range of similarity indexes are to some extent the same for these patients. In figure 8, the bins with similarity index value more than 0.8 have very low counts, meaning that the non-auditory alpha sources are still active and contribute to global alpha power at the sensor level. The ideal situation would be that all non-auditory alpha sources are inactive. This would lead to a maximum similarity index as shown in the simulated data section. Relative alpha power of each cortical brain region (figure 9) shows that, although the similarity method effectively reduces the contribution of alpha power of some of the non-auditory cortices to the alpha power calculated on the sensor level, the increase in TFPs is not accompanied by an increase in alpha power in the right auditory cortex.

The increase in TPFs leads to less alpha contribution of non-auditory areas at the electrode level. However, increasing alpha source power in the auditory regions is a matter of training. The reason behind alpha power having not increased in all regions of interest might be low similarity indices in these three visits. More sessions should solve that problem as in all skill-learning procedures characterizing neurofeedback learning [40]. With increasing session number, the specificity and anatomical focus of the change becomes more specific and circumscribed.

6. Conclusion

A new method for on-line detection of auditory alpha EEG-activity originating from primary auditory cortex is proposed and tested with simulated data and illustrated with patient data. The aim of the proposed procedure is its use in an EEG-neurofeedback-treatment approach allowing on-line auditory alpha self-regulation training in patients with chronic tinnitus. The algorithm should allow on-line detection of the alpha-rhythm in the auditory cortex hidden behind temporal lobe structures and facilitate feedback of this auditory alpha. To suppress superposition of auditory alpha by somatosensory and visual alpha, we used a continuous tactile jaw-stimulation and visual stimulation protocol to suppress somatosensory alpha of regions adjacent to auditory cortex and visual alpha for regulation of auditory alpha activity. Using simulated data in auditory and non-auditory brain regions and three tinnitus patients as examples, we demonstrated the feasibility of the algorithm and the procedure for auditory alpha neurofeedback.

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Conflict of interest

The authors state that no conflicts of interest regarding this manuscript exist.

ORCID iDs

Azim Malekshahi https://orcid.org/0000-0002-5367-1604

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