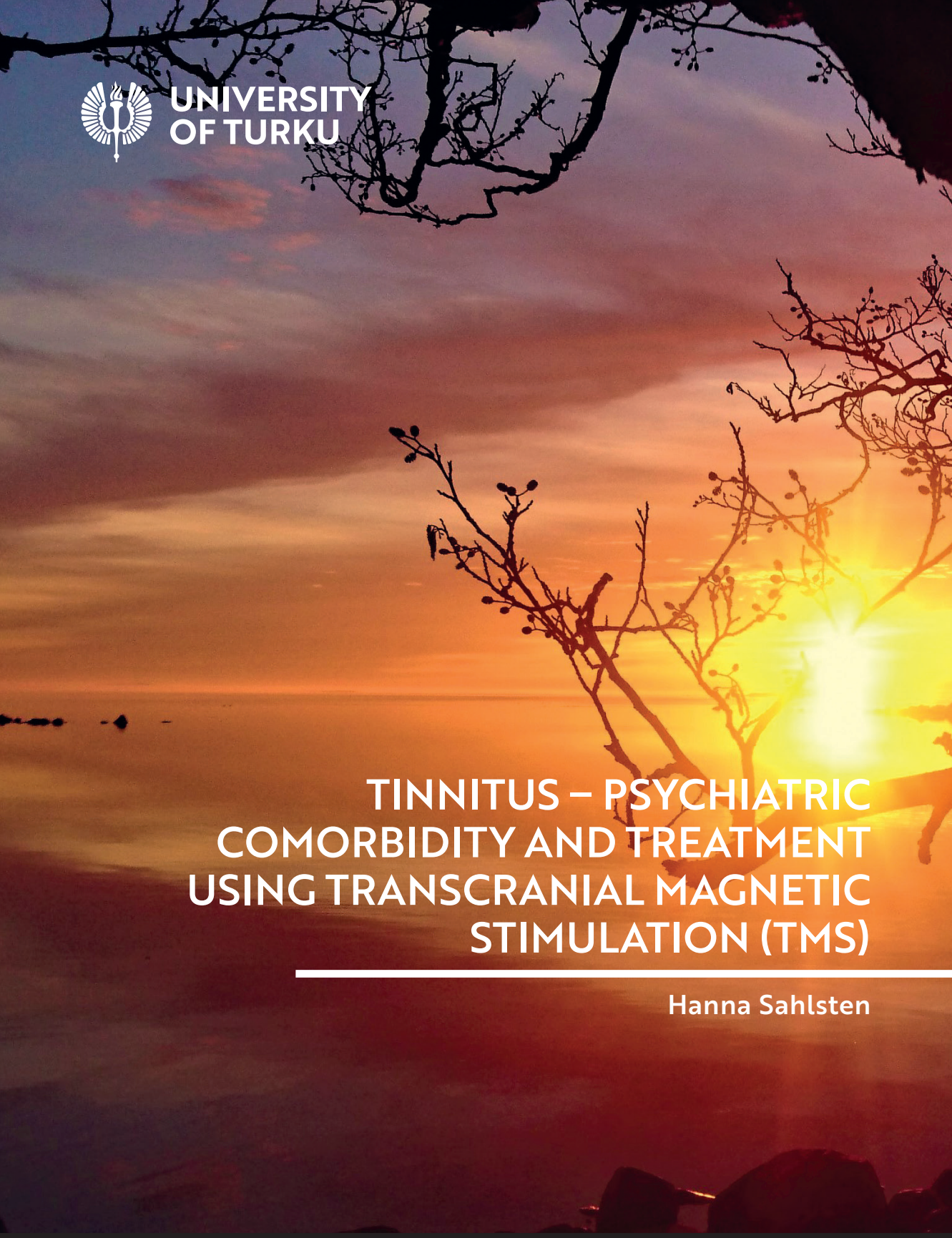

UNIVERSITY OF TURKU

TINNITUS – PSYCHIATRIC COMORBIDITY AND TREATMENT USING TRANSCRANIAL MAGNETIC STIMULATION (TMS)

Hanna Sahlsten

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
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ABSTRACT

Hanna Sahlsten

TINNITUS – PSYCHIATRIC COMORBIDITY AND TREATMENT USING TRANSCRANIAL MAGNETIC STIMULATION (TMS)

University of Turku, Faculty of Medicine, Department of Clinical Medicine, Department of Clinical Neurophysiology; Turku Doctoral Programme in Clinical Research; Division of Clinical Neurosciences, Turku University Hospital
Annales Universitatis Turkuensis Ser. D – Turku, Finland 2019

Tinnitus is the perception of sound in the absence of any external noise. It severely impairs the quality of life in 1-2% of people. Tinnitus is frequently associated with depression, anxiety, and insomnia. The exact pathophysiology of tinnitus is still unclear. No curative therapy exists for chronic tinnitus, and treatment focuses on symptomatic relief.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neuromodulation technique that is used for treating depression and neuropathic pain. The evidence of its efficacy for chronic tinnitus is still inconclusive, and the optimal treatment protocols are thus still obscure.

This thesis aimed to further evaluate the use of rTMS for chronic tinnitus and investigate the psychiatric comorbidity of tinnitus patients. The first (open pilot) study utilized electric field (E-field) navigated rTMS for very severe chronic tinnitus with promising results. In the second (randomized placebo-controlled) study, the effects of 1-Hz E-field rTMS targeted according to the tinnitus pitch to the left auditory cortex were analyzed. Despite the significant improvements in tinnitus, active rTMS was not superior to the placebo, possibly due to large placebo-effect and wide inter-individual variation in treatment efficacy. The third study on parallel groups compared the effects of neuronavigated rTMS to non-navigated rTMS (based on the 10-20 EEG localization system). Both groups benefitted from the treatment, but the method of coil localization was not a critical factor for treatment outcome. In the fourth study, current and lifetime DSM-IV diagnoses of Axis I (psychiatric disorders) and Axis II (personality disorders) were assessed in tinnitus patients using structured clinical interviews (SCID-I and -II). Tinnitus patients were prone to episodes of major depression, and they often had obsessive-compulsive personality features. Psychiatric disorders in this study seemed to be comorbid or predisposing conditions rather than the consequences of tinnitus.

Keywords: Tinnitus, transcranial magnetic stimulation, neuronavigated, psychiatric disorder, personality disorder, SCID

TIIVISTELMÄ

Hanna Sahlsten

TINNITUS – PSYKIATRINEN SAIRASTAVUUS JA HOITO TRANSKRANIAALISELLA MAGNEETTISTIMULAATIOLLA (TMS)

Turun yliopisto, Lääketieteellinen tiedekunta, Kliininen laitos, Kliinisen neurofysiologian oppiaine; Turun kliininen tohtoriohjelma; Turun Yliopistollisen keskussairaalan neurotoimialue
Turun yliopiston julkaisuja Ser. D – Turku, Suomi 2019

Tinnituksen ääniaistimus syntyy ilman ulkoista äänilähdettä. Se heikentää vakavasti elämänlaatua 1-2%:lla ihmisistä. Tinnitus yhdistetään usein masennukseen, ahdistukseen ja unettomuuteen. Tinnituksen tarkka syntymekanismi on vielä epäselvä. Pitkäaikaiselle tinnitukselle ei ole parantavaa hoitoa, vaan hoidossa keskitytään oireiden lievittämiseen.

Transkraniaalinen magneettistimulaatio sarjapulssein (rTMS) on kajoamaton aivojen toimintaa muokkaava menetelmä, jota käytetään masennuksen ja hermoperäisen kivun hoidossa. Sen teho pitkäaikaiseen tinnitukseen on vielä epävarmaa ja optimaaliset hoitoprotokollat ovat selvittämättä.

Tämän väitöskirjan tavoitteena oli arvioida rTMS:n käyttöä pitkäaikaisen tinnituksen hoidossa ja lisäksi tutkia tinnituspotilaiden psykiatrista sairastavuutta. Ensimmäisessä osatyössä (avoin pilotti) käytettiin sähkökenttäohjattua (E-field) navigoivaa rTMS:a pitkäaikaiseen, erittäin vaikeaan tinnitukseen lupaavin tuloksin. Toisessa osatyössä (satunnaistettu lumekontrolloitu) arvioitiin tinnitusäänen korkeuden mukaan vasemmalle kuuloaivokuorelle suunnatun 1-Hz:n sähkökentän mukaan navigoidun rTMS:n vaikutuksia. Vaikka tinnitus helpottui merkittävästi, ei aktiivi-rTMS ollut lumehoitoa parempi, mahdollisesti johtuen suuresta lumevaikutuksesta ja laajasta yksilöiden välisestä vaihtelusta hoidon tehossa. Kolmannessa osatyössä verrattiin rinnakkaisryhmien välillä neuronavigoidun rTMS:n ja sokko rTMS:n (10-20 EEG-systeemiin perustuva paikannus) vaikutuksia. Molemmat ryhmät hyötyivät hoidosta, eikä kelan paikannusmenetelmä ollut ratkaiseva tekijä hoidon lopputuloksen kannalta. Neljännessä osatyössä nykyiset ja elämänaikaiset akselin I (psykiatriset häiriöt) ja akselin II (persoonallisuushäiriöt) DSM-IV diagnoosit määritettiin tinnituspotilailta käyttäen strukturoituja psykiatrisia haastatteluja (SCID-I ja -II). Tinnituspotilaat olivat alttiita vakaville masennusjaksoille ja heillä oli usein vaativan persoonallisuuden piirteitä. Psykiatriset häiriöt vaikuttivat olevan ennemmin samanaikaisia tai altistavia tiloja kuin tinnituksen seurauksena ilmaantuneita häiriöitä.

Avainsanat: Tinnitus, transkraniaalinen magneettistimulaatio, neuronavigoitu, psykiatrinen häiriö, persoonallisuushäiriö, SCID

TABLE OF CONTENTS

ABBREVIATIONS

AC	Auditory cortex
ACC	Anterior cingulate cortex
ACS	Auditory cortex stimulation
BAEP	Brainstem auditory evoked potentials
BDI	Beck Depression Inventory
BDNF	Brain derived neurotrophic factor
CBT	Cognitive behavioral therapy
CI	Cochlear implant
CI	Confidence interval (in the Statistical analyses)
cMAP	Compound muscle action potential
CN	Cochlear nucleus
CT	Computed tomography
dB	Decibel
dB HL	Decibel Hearing Level
DBS	Deep brain stimulation
DES	Dissociative Experiences Scale
DLPFC	Dorsolateral prefrontal cortex
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
EEG	Electroencephalography
E-field	Electric field
ENT	Ear, Nose and Throat
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
GET	Gaze-evoked tinnitus
GIC	Global Impression of Change
HF rTMS	High frequency repetitive transcranial magnetic stimulation (> 5 Hz)
HG	Heschl's Gyrus
HLMM	Hierarchical linear mixed model
Hz	Hertz
ICC	Inferior colliculus
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th revision
ITLD	Intratympanic lidocaine and dexamethasone injections
JSEQ	Jenkins Sleep Evaluation Questionnaire
LF rTMS	Low frequency repetitive transcranial magnetic stimulation (≤ 1 Hz)
LTD	Long-term depression
LTP	Long-term potentiation
MCS	Motor cortex stimulation
MD	Major depression

MEP	Motor evoked potential
MRI	Magnetic resonance image
NAc	Nucleus accumbens
NCS-R$_{\text{-survey}}$	The US National Comorbidity Survey Replication
NMDA	N-methyl-D-aspartate
NRS	Numeric Rating Scale
nrTMS	Neuronavigated repetitive transcranial magnetic stimulation
OAE	Otoacoustic emissions
O-CPD	Obsessive-compulsive personality disorder
PD	Personality disorder
PET	Positron emission tomography
PTA	Pure tone average
RCT	Randomized controlled trial
RMT	Resting motor threshold
rTMS	Repetitive transcranial magnetic stimulation
SatKS	Satakunta Central Hospital
SCID	Structured Clinical Interview for DSM Disorders
SCL-90	Symptom Checklist-90
SD	Standard deviation
SE	Standard error
SOAE	Spontaneous otoacoustic emission
SOC	Superior olivary complex
SSRI	Selective serotonin reuptake inhibitor
STG	Superior temporal gyrus
tDCS	Transcranial direct current stimulation
TENS	Transcutaneous electrical nerve stimulation
THI	Tinnitus Handicap Inventory
TM	Target marker
TMS	Transcranial magnetic stimulation
TRT	Tinnitus Retraining Therapy
TS	Target stimulus
TUCH	Turku University Hospital
tVNS	Transcutaneous vagus nerve stimulation
VAS	Visual Analog Scale
VCNS	Chronic electrical vestibulocochlear nerve stimulation
vmPFC	Ventromedial prefrontal cortex
VNS	Vagus nerve stimulation
V/m	Volts per meter (E-field strength)
WHO	World Health Organization

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, which are referred to in the text by Roman numerals I-IV:

I Sahlsten H, Isohanni J, Haapaniemi J, Salonen J, Paavola J, Löyttyniemi E, Johansson R, Jääskeläinen SK. Electric field navigated transcranial magnetic stimulation for chronic tinnitus: A pilot study. Int J Audiol. 2015;54(12):899-909. doi: 10.3109/14992027.2015.1054041. Epub 2015 Jun 18.

II Sahlsten H, Virtanen J, Joutsa J, Niinivirta-Joutsa K, Löyttyniemi E, Johansson R, Paavola J, Taiminen T, Sjösten N, Salonen J, Holm A, Rauhala E, Jääskeläinen SK. Electric field-navigated transcranial magnetic stimulation for chronic tinnitus: A randomized, placebo-controlled study. Int J Audiol. 2017 Sep;56(9):692-700. doi: 10.1080/14992027.2017.1313461. Epub 2017 Apr 18.

III Sahlsten H, Holm A, Rauhala E, Takala M, Löyttyniemi E, Karukivi M, Nikkilä J, Ylitalo K, Paavola J, Johansson R, Taiminen T, Jääskeläinen SK. Neuronavigated versus non-navigated repetitive transcranial magnetic stimulation for chronic tinnitus: A randomized study. Trends in Hearing 2019;23:1-14. doi: 10.1177/2331216518822198.

IV Sahlsten H, Taiminen T, Karukivi M, Sjösten N, Nikkilä J, Virtanen J, Paavola J, Joutsa J, Niinivirta-Joutsa K, Takala M, Holm A, Rauhala E, Löyttyniemi E, Johansson R, Jääskeläinen SK. Psychiatric (Axis I) and personality (Axis II) disorders and subjective psychiatric symptoms in chronic tinnitus. Int J Audiol. 2018 Apr;57(4):302-312. doi: 10.1080/14992027.2017.1409440. Epub 2017 Nov 30.

1 INTRODUCTION

In tinnitus, a disturbing sound is perceived in the absence of external noise. It is a common disorder with a prevalence of 10–15% in the general population. Most people habituate to the phantom sound, but 1–2% of the people suffer from chronic intractable tinnitus that causes anxiety, sleep, or concentration difficulties and considerable distress in daily living (Langguth et al. 2013). It is notable that severe tinnitus in depressed patients can even lead to suicide (Dobie 2003). Tinnitus, similarly to pain, is a purely subjective experience that is only appraised by self-evaluation (Henry et al. 2005).

Tinnitus is currently viewed as a complex condition involving multiple brain networks while its exact pathophysiology still remains obscure. Recent research implies that tinnitus results from maladaptive plasticity in the central auditory network associated with hearing loss and deafferentation of the auditory cortex (AC). Abnormal hyperactivity is generated within the AC and auditory brainstem nuclei following cortical deafferentation, and functional reorganization occurs after injury to the cochlea or auditory nerve (Henry et al. 2014). Further, neuroimaging studies have also shown increased activity in non-auditory areas, such as the frontal, parietal, limbic areas, and frontostriatal loops of the brain (Leaver et al. 2011; Rauschecker et al. 2015).

The treatment of chronic tinnitus is challenging, as no curative therapy currently exists, although nearly 60 different treatment modalities have been tried (Zenner et al. 2017). The treatment focuses only on symptomatic relief. Usually, specific tinnitus counseling and cognitive behavioral therapy are recommended. Possible concurrent depression should be treated, but routine use of anti-depressive or other medication should be avoided (Tunkel et al. 2014). The clinical evidence indicates that hearing aids provide a benefit by making the patient less aware of tinnitus, as the sound environment is enriched, and communication enhanced by amplifying the sounds (Del Bo & Ambrosetti 2007).

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neuromodulation technique that applies magnetic pulses to the scalp and underlying brain to induce electric field currents and alterations in neuronal excitability and neurotransmitter systems (Allen et al. 2007; Moisset et al. 2016; Lamusuo et al. 2017). Cortical excitability can be increased using high-frequency or decreased using low-frequency rTMS via long-term potentiation or long-term depression-like effects in synaptic transmission (Hoogendam et al. 2010). RTMS also induces widespread functional changes in the brain networks connected to the stimulated cortical target, and further, releases dopamine and endogenous opioids

(Hoogendam et al. 2010; Lamusuo et al. 2017; Lefaucheur et al. 2014; Moisset et al. 2016). The AC is hyperactive in tinnitus, and therefore, a low frequency (≤ 1 Hz) rTMS that reduces cortical excitability, has been suggested for the treatment of tinnitus (Plewnia et al. 2007; Lefaucheur et al. 2014).

Over the past decade, depression and neuropathic pain have been successfully and safely treated with rTMS (Lefaucheur et al. 2014; Cruccu et al. 2016; Rossi et al. 2007). However, in chronic tinnitus, the evidence is still controversial, although a recent meta-analysis has concluded there is moderate efficacy for low-frequency rTMS (Soleimani et al. 2016). Several placebo-controlled studies have demonstrated the efficacy of rTMS for tinnitus over the temporoparietal regions (Khedr et al. 2008; Anders et al. 2010; Marcondes et al. 2010; Mennemeier et al. 2011; Folmer et al. 2015), while others have shown no significant efficacy over sham (Plewnia et al. 2012; Hoekstra et al. 2013; Piccirillo et al. 2013; Langguth et al. 2014; Landgrebe et al. 2017). Further, the role of neuronavigated rTMS (nrTMS) for tinnitus treatment remains an open question, as well as do the optimal treatment parameters (Langguth et al. 2014). In addition, very little is known about the long-term effects of rTMS on tinnitus.

Tinnitus has been associated with an increased rate of psychiatric disorders, but the reported frequencies vary vastly (Geocze et al. 2013; Pattyn et al. 2016; Pinto et al. 2014). Most of the studies so far have used only self-report symptom questionnaires that are not validated for diagnostic evaluation, thus causing these considerably fluctuating prevalence rates. Only a few studies have investigated psychiatric disorders in tinnitus patients using a structured diagnostic interview. The difference in these methods is crucial, as the detection of psychiatric symptoms using self-report scales does not automatically mean that the diagnostic criteria for a psychiatric disorder are actually fulfilled.

In this thesis, the feasibility and effects of rTMS for chronic tinnitus were evaluated, including the influence of several factors that relate to stimulation protocol. The long-term effects of rTMS for up to 6 months were also assessed. In addition, nrTMS was compared to non-navigated rTMS to evaluate the role of neuronavigation in the efficacy of rTMS for tinnitus control. To further analyze the tinnitus patients, the current and lifetime prevalence of psychiatric disorders were evaluated using a structured diagnostic interview (SCID-I and -II), and the temporal relationship of psychiatric disorders and the occurrence of tinnitus symptom were also examined. Further, current psychiatric symptoms using self-report questionnaires were assessed, as well as quality of life measures.

2 REVIEW OF THE LITERATURE

2.1 The anatomy and neurophysiology of the auditory system

The auditory system consists of the outer ear (the pinna and the ear canal); the middle ear (an air-filled chamber with the three ossicles: malleus, incus, and stapes); the inner ear (the cochlea: hair cells, basilar membrane and spiral ganglion); the auditory nerve; and the central auditory nervous system. The auditory nervous system (Figure 1) consists of structures in the pons, midbrain, thalamus, and cerebral cortex. When considering tinnitus, the most crucial parts of the auditory system are the central auditory pathways. (Moller 2011)

Sound waves travel through the ear canal and induce a vibration of the tympanic membrane, the ossicles, the perilymph, and the basilar membrane (to the inner and outer hair cells) of the cochlea. Mechanical movement of the basilar membrane is transduced by an inner row of hair cells that releases neurotransmitter (glutamic acid) onto the dendrites of afferent neurons that then travel to the spiral ganglion and form the auditory nerve. (Ryan & Bauer 2016)

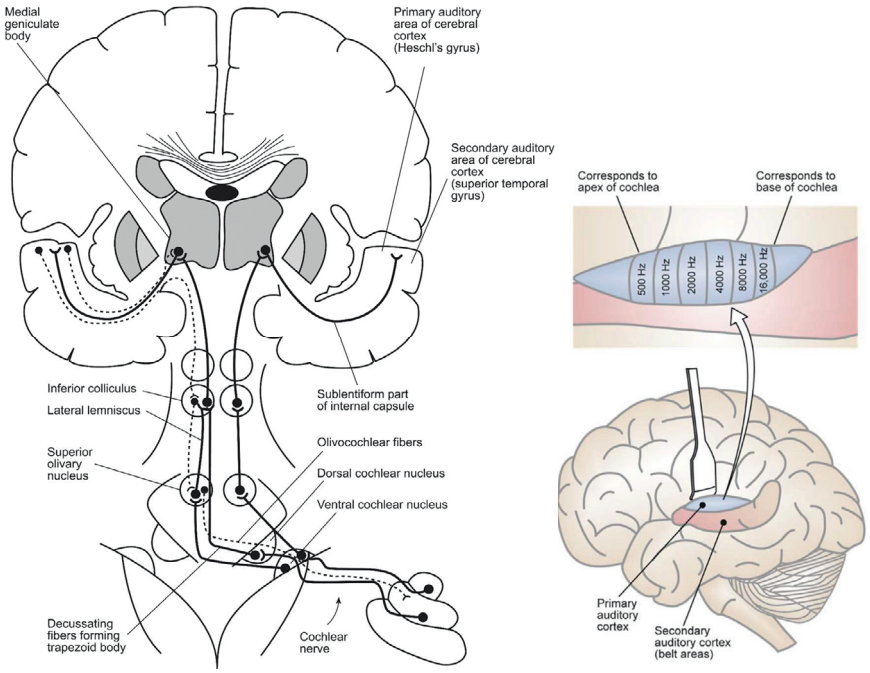
The cochlea is composed of an osseous labyrinth, a fluid-filled tunneled compartment that travels approximately 2 and 3/4 revolutions around its longitudinal axis and lies within an osseous capsule of the temporal bone. The range of frequencies is tonotopically distributed along the cochlea from the base (high frequencies) to the apex (low frequencies), and this tonotopy continues along the auditory pathway up to the auditory cortex (AC) (Figure 1b). The scala media (cochlear duct) contains endolymph and is a compartment that is enclosed by the membranous labyrinth. The cochlear duct includes a row of inner hair cells and three rows of outer hair cells laid out along the basilar membrane, along with supporting elements that form the organ of Corti, which is the sensorineural end organ for hearing. (Raphael & Altschuler 2003)

The inner hair cells (approximately 3500 per cochlea) conduct the “actual hearing” by transducing and initiating the depolarization of the spiral ganglion neurons. The outer hair cells act as accessory sensory cells that enhance the sensitivity of the cochlea. Injured inner hair cells do not regenerate. Neural feedback loops that transfer efferent signals to the outer hair cells assist in sharpening and amplifying the auditory signals. The stria vascularis produces an endocochlear potential and sustains the ionic composition of the endolymph. The membranous labyrinth is surrounded by an additional fluid space that is filled with perilymph forming the scala vestibuli and the scala tympani. (Raphael & Altschuler 2003)

The afferent fibers of the auditory nerve terminate in the cochlear nucleus (CN) in the medulla. The CN has three main parts: the anterior ventral, the posterior ventral, and the dorsal cochlear nucleus. There are two different ascending pathways from the CN to the auditory cortices: the classical (lemniscal) pathway and the non-classical (extralemniscal) pathway. The auditory pathways receive input from the somatosensory system at the inferior colliculus (ICC) and the dorsal CN. In addition, there are two descending pathways that pass via the nuclei of the auditory pathways and reach caudally down to the receptors in the cochlea. (Moller 2011)

In the classical auditory pathway, some auditory signals travel from the CN to the ipsilateral superior olivary complex (SOC) of the medulla; however, most signals do cross to the contralateral side. The bilateral SOCs have connections with each other through the trapezoid body. The ascending auditory neural tract continues from the SOC to the lateral lemniscus (along which lays the nucleus of the lateral lemniscus which also has connections to the contralateral nuclei) and to the ICC and then farther still to the medial geniculate body in the thalamus. There are abundant connections between the right and left ICCs at the midbrain level. Through the auditory thalamocortical radiations, auditory signals travel to the AC in the superior temporal gyrus (STG), which contains ipsilateral and contralateral connections. Thus, sounds are represented bilaterally at the AC (Lin & Staecker 2006). The AC can be divided into a deeper situated primary AC in the transverse temporal gyrus, the Heschl's gyrus (HG), and the more superficial secondary AC in the STG. Further, as mentioned earlier, frequencies are tonotopically distributed along the cochlea, and this tonotopy continues along the auditory pathway up to the AC; high frequencies are represented in the more posterior and lower frequencies in the anterior areas (Moerel et al. 2014). Figure 1 shows the main central auditory pathways.

The non-classical auditory pathway differs from the classical pathway at several levels, but the main differences are in the thalamus, which plays a crucial role in auditory processing. The thalamus has a ventral part that belongs to the classical pathway and projects to the primary (and secondary) AC. The other parts of the thalamus, the medial and dorsal parts, belong to the non-classical pathway, connecting directly to the secondary AC, as well as, subcortically to other parts of the brain, such as the striatum and amygdala. These connections provide for an auditory stimulus a route to the emotional brain. Another difference between the pathways is that while neurons in the classical pathway only respond to one sensory modality, some multisensory neurons in the non-classical pathway also respond to other sensory modalities, such as the somatosensory or visual. (Moller 2011)



a. b.

Figure 1. The central auditory pathways. Figure 1a illustrates the major central auditory pathways from the cochlea to the auditory cortex. Solid colored lines show the ascending (afferent) pathways to the primary auditory cortex and the descending (efferent) connections are presented by broken lines. Modified from (Lin & Staecker 2006). Figure 1b illustrates the different pitches that are tonotopically represented within the auditory cortex: High frequencies are represented in the posterior and lower frequencies in the anterior area. Reproduced with the permission of the copyright holders (Sahlsten et al. 2015).

The descending auditory pathways are extensive, especially the cortico-thalamic pathways, and they are mainly reciprocal to the ascending pathways (Figure 1). However, only little is known about their function. The axons of the most peripheral parts (olivocochlear bundle) of this pathway terminate mostly on the outer hair cells of the cochlea, and thus descending pathways can influence the frequency selectivity and auditory sensitivity of hearing. (Moller 2011)

2.2 Definition and prevalence of tinnitus

Tinnitus is defined as the perception of sound in the absence of any external noise. That sound can be hissing, sizzling, ringing or even musical, but in contrast to auditory hallucinations, the sound involves no meaning. Tinnitus can be constant or intermittent, pulsatile or non-pulsatile, and patients may experience more than one type of sound. Tinnitus can be localized to one or both ears or centrally within the head. It is also divided into objective and subjective subtypes. Subjective tinnitus is perceived only by the patient, whereas objective tinnitus caused by e.g., stenotic pulsating vessels, is detectable by another observer, usually by auscultation. (Baguley et al. 2013; Langguth et al. 2013)

Tinnitus can also be divided into primary and secondary. Primary tinnitus is subjective, idiopathic, and may or may not be associated with hearing loss, while secondary tinnitus is associated with a specific underlying cause (other than hearing loss) or a specific organic condition. Further, tinnitus is divided into recent onset (less than 6 months in duration) or persistent/chronic (6 months or longer in duration). Tinnitus may be bothersome, affecting the quality of life and general health, causing the patient to seek treatment, or it can be nonbothersome having no significant effect on the patient's life. (Tunkel et al. 2014)

Tinnitus affects approximately 10-15% of the population, and it seems to be a global burden (Henry et al. 2005). Most people habituate to the phantom sound, but tinnitus does severely impair the quality of life of about 1–2% of the population (Langguth et al. 2013). In a large Norwegian survey, 21.3% of men and 16.2% of women reported some perception of tinnitus, with 4.4% of these men and 2.1% of the women reporting high symptom intensity (Krog et al. 2010). Similarly, a large U.S study discovered 26.1% of men and 24.6% of women having some tinnitus, with 9.4% of these men and 6.5% of the women having frequent tinnitus (Shargorodsky et al. 2010).

The prevalence of troublesome tinnitus increases with age, as hearing impairment is also more common in elderly people. A Finnish study of tinnitus in people age 70-85 years discovered that 26.4% of women and 31.6% of men were experiencing tinnitus with annoyance, whereas 30.3% and 33.3% of this group had tinnitus without annoyance, respectively (Salonen et al. 2007). As people in general are now getting older in the Western world, and professional/leisure noise exposure is increasing, tinnitus prevalence is expected to continue to increase in the future (Roberts et al. 2010).

2.3 The pathophysiology of tinnitus

2.3.1 Primary tinnitus - Causal factors and alterations in the auditory and central nervous systems

Primary tinnitus is currently considered a complex disorder that involves auditory and multiple other brain networks while its exact pathophysiology is still obscure. Otological disorders, especially high-frequency sensorineural hearing loss, present one of the major risk factors for tinnitus. In cochlear damage, a loss of the cochlear hair cells (in a certain frequency range) occurs. This loss may be due to any cause, such as noise, ototoxic agents, aging, or even genetic factors. The tinnitus pitch match has been shown to be associated with the frequency spectrum of hearing loss, thereby suggesting the relevance of hearing impairment for the generation of tinnitus (Schecklmann et al. 2012).

Cochlear pathology is not always visible in the audiogram of tinnitus patients, but it may be diagnosed by more sensitive audiological measures, like otoacoustic emissions (OAE) (Mckee & Stephens 1992) or brainstem auditory evoked potentials (BAEP) (Schaette & McAlpine 2011). Although cochlear injury could be the initial source of tinnitus, later neural changes in the central auditory system, such as increased activity of the AC, are more likely to maintain the condition and lead to chronic tinnitus. Research indicates that tinnitus may be generated via dysfunctional or maladaptive activation of neural plasticity that is induced by an altered sensory input, mainly auditory deprivation associated with a hearing deficit (Henry et al. 2014). The signs of this neural deafferentation have also been shown to be present in tinnitus patients with audiometrically normal hearing (Weisz et al. 2006).

Different mechanisms can cause dysfunctional neural changes after a cochlear injury. An increased spontaneous firing rate of neurons in the central auditory network represents one possible cause for tinnitus. Cochlear hearing loss or injury reduces cochlear nerve activity, causing a downregulation of inhibitory cortical processes, and leading to hyperexcitability within the central auditory structures, especially in the primary AC (Noreña & Eggermont 2003). However, tinnitus is not just a straightforward correlate of the imbalance of firing patterns across the tonotopic array of the injured cochlea, since tinnitus sound can persist even when the input from the ear is blocked by cutting off the auditory nerve (Jackson 1985; Baguley et al. 2013).

Another possible mechanism for tinnitus is neural synchrony. Temporal synchrony in the firing pattern increases immediately after noise-induced hearing deficit across several neurons in the primary AC, especially in those neurons representing

the affected part of the tonotopic region (Noreña & Eggermont 2003; Seki & Eggermont 2003). A hearing defect at a certain frequency zone induces disturbed tonotopy in the primary AC, thereby causing the neurons with characteristic frequencies within the deprived region to adopt the tuning features of their less-affected neighbours (Eggermont & Komiya 2000). Therefore, tonotopic map reorganisation follows, and the hearing deficit frequency zone is less presented in the AC while the neighbouring non-affected frequencies are over-presented (Wienbruch et al. 2006).

The theory of changed neural synchrony in tinnitus is supported by studies that have reported altered oscillatory brain activity in tinnitus patients (Mueller et al. 2013). The change in oscillatory activity in tinnitus has been reported as a reduction in the alpha band (8-12 Hz) electroencephalography (EEG) activity in the AC (Weisz et al. 2005) or an increase in the delta (2–4 Hz) (Weisz et al. 2005), the theta (4–8 Hz) (Moazami-Goudarzi et al. 2010), the beta (12–30 Hz) (Moazami-Goudarzi et al. 2010) or the gamma (30–100 Hz) (van der Loo et al. 2009) bands compared to the controls without tinnitus. On a subcortical level, abnormal low-frequency activity in the thalamus associates with impairment in the thalamo-cortic-thalamic network, thus influencing the perception of tinnitus, as in other neuropsychiatric conditions (Fuggetta & Noh 2013).

Map reorganisation in the AC after a hearing deficit has also been compared to map reorganisation in the somatosensory cortex after amputation (Flor et al. 1995; De Ridder et al. 2011a). A proposed model implies that sensory deafferentation induces neuroplastic changes (cortical disinhibition with increased plasticity and reorganization), resulting in an increased activation of the primary sensory cortex, which is the somatosensory cortex in phantom pain and the AC in tinnitus. Awareness of this stimulus emerges only when this increased local activity is connected to a wider cortical perceptual network that involves the frontal, parietal, and limbic brain areas. Thus, increased activity in the AC following auditory deprivation is necessary, but not alone sufficient enough, to create tinnitus perception. Through learning mechanisms, the phantom perception associates with distress, and activates a nonspecific distress network consisting of the anterior cingulate cortex (ACC), anterior insula, and amygdala. (Langguth et al. 2013)

Further, attentional and memory mechanisms play an important role in the persistence of the awareness of tinnitus, as well as in the difficulty of the associated distress (De Ridder et al. 2011a). The brain networks involved in the phantom perception of tinnitus are shown in Figure 2. Especially, tinnitus and pain both are gating disorders that have a dysfunctional frontostriatal loop system (Figure 5) (Rauschecker et al. 2015). It is notable, that neuroimaging findings have supported these ideas by showing that not only the central auditory system, but also the

prefrontal and emotional networks, are involved in the pathophysiology of tinnitus (Lanting et al. 2009).

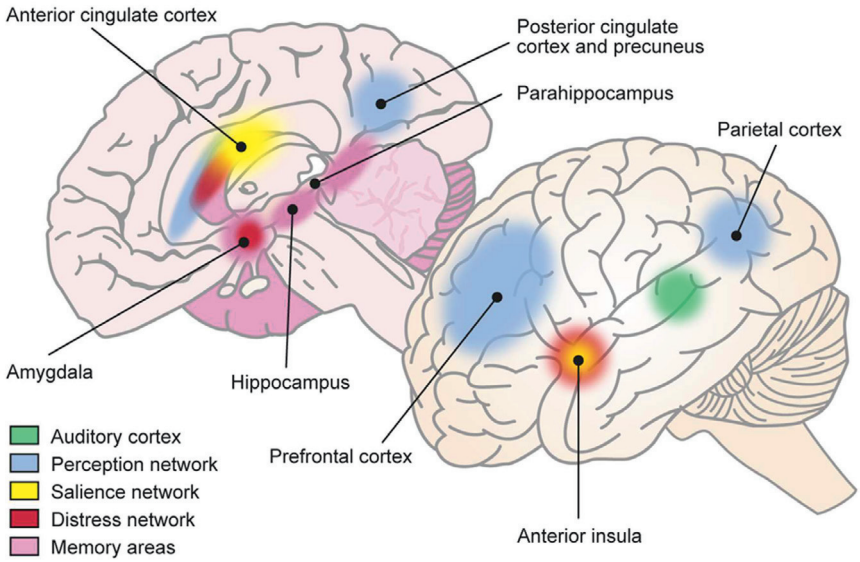


Figure 2. Brain networks involved in the phantom perception of tinnitus. Increased activity in the auditory cortex (green) following auditory deprivation is necessary, but not sufficient alone, for tinnitus perception. The patient becomes aware of the tinnitus stimuli if the auditory activity is connected to a larger awareness network involving the subgenual and dorsal anterior cingulate cortices, posterior cingulate cortex, precuneus, parietal cortex, and prefrontal cortex (blue). Salience to the phantom perception is presented by the activation of the dorsal anterior cingulated cortex and anterior insula (yellow). Tinnitus annoyance is presented by a coactivation of a non-specific distress network involving the anterior cingulate cortex (subgenual and dorsal anterior cortical cortices), anterior insula, and amygdala (red). Memory mechanisms involving the parahippocampal area, amygdala, and hippocampus will affect the persistence of the phantom perception (purple). Modified from (Langguth et al. 2013).

One neurophysiological model of tinnitus is based on improper activation of the limbic and the sympathic part of the autonomic nervous system by the tinnitus signal (Figure 3) (Jastreboff & Hazell 1999). Attention, distraction, and sensory gating operates dysfunctionally, leading to difficulties in excluding the signal from consciousness and to an impaired habituation. This causes symptoms like anxiety, concentration difficulties, panic attacks, and a diminished ability to enjoy life. The same reactions are observed after overstimulation of the limbic and autonomic

nervous system by chronic pain, sensory stimulation, or sleep deprivation (Jastreboff & Jastreboff 2006).

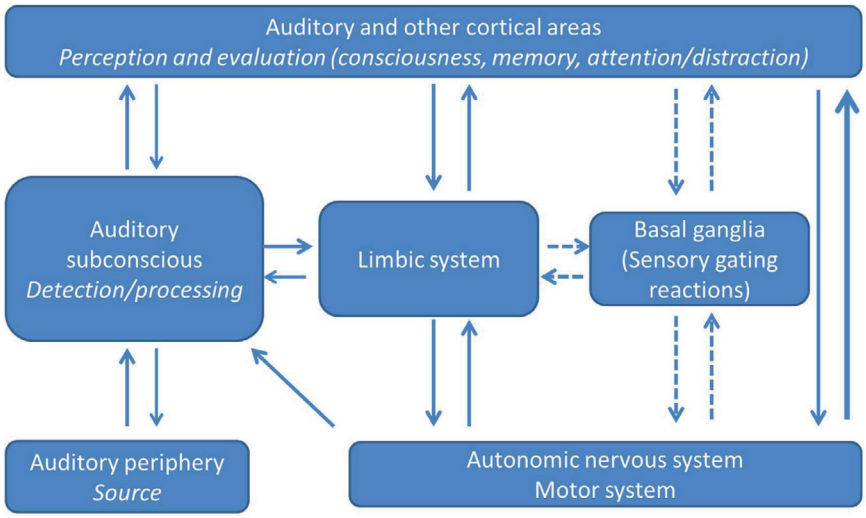


Figure 3. The neurophysiological model of tinnitus. Modified from (Jastreboff & Hazell 1999).

As mentioned previously, tinnitus-related activity changes occurring in the central nervous system are not restricted to auditory pathways, but alterations in the networks of both auditory and non-auditory structures have been detected (Schlee et al. 2008; Schlee et al. 2009). Tinnitus-related functional and anatomical anomalies have been assessed by using functional magnetic or positron emission tomography (PET) imaging. Leaver et al. (2011) have reported both functional and structural markers of chronic tinnitus in the auditory and limbic regions of the brain. They detected moderate hyperactivity in the primary and posterior ACs of tinnitus patients with the nucleus accumbens (NAc) exhibiting the greatest degree of hyperactivity. They also discovered structural differences in the ventromedial prefrontal cortex (vmPFC), which is strongly connected to the NAc. In their study, tinnitus-related anomalies were intercorrelated in the two limbic regions and between the limbic and primary auditory areas, thus emphasizing the importance of auditory-limbic connections in chronic tinnitus (Leaver et al. 2011). Further, it has been suggested that the limbic system (basal ganglia including NAc and ventral striatum) actually effectively switches on and off some of the perceived signals, rather than just colouring those signals (Rauschecker et al. 2010; Rauschecker et al. 2015). While many brain regions have been associated with tinnitus, the

association of the cerebellum with tinnitus is not to date substantially supported by the current neuroimaging studies (Lanting et al. 2009).

There might also be additional tinnitus generating mechanisms, based on the severity of the hearing deficit. The Bayesian brain model suggests that the brain can be viewed as a probability machine that continuosly makes predictions about the world and then updates them based on what it receives from the senses. Further, its main function is to reduce environmental uncertainty (De Ridder et al. 2014b). The model assumes the existence of two different kinds of tinnitus, depending on the degree of the hearing deficit, namely, an AC -related form of tinnitus not associated with a hearing deficit, and a (para)hippocampal form associated with a hearing deficit, in which the AC might be of only little importance. This theory has been verified in at least one study that analyzed the EEG recordings of tinnitus patients, and made correlations to the mean hearing deficit, the range of the hearing deficit, and the hearing deficit at the tinnitus frequency (Vanneste & De Ridder 2016). In this study, in patients with minor or no hearing deficit, tinnitus was more related to the AC activity, but not to (para)hippocampal memory- related activity, whereas in tinnitus patients with more severe hearing deficit, tinnitus seemed to be associated with the (para)hippocampal function. Vanneste and De Ridder (2016) also stated that the hearing deficit seemed to drive the communication between the AC and the parahippocampus. These findings are in line with the proposed model that presents a theoretical multiphase compensation mechanism at the cortical level and has been hypothesized linking auditory deafferentation to tinnitus (Vanneste & De Ridder 2016).

Tinnitus-related anatomical changes have been assessed by using magnetic resonance image (MRI) voxel-based morphometry (Landgrebe et al. 2009). Landgrebe et al discovered significant grey matter decreases in the right ICC and in the left hippocampus of tinnitus patients. Further, (outside the auditory system) gray-matter decrease in the subcallosal area (including the nucleus accumbens) and gray-matter increase at the thalamic level (within the auditory pathways) have also been observed in chronic tinnitus (Muehlau et al. 2006). Gray-matter decrease in the subcallosal area including basal ganglia is relevant, because it is known to process acoustically induced unpleasant emotions (Blood et al. 1999). Thus, the involvement of both sensory and striatolimbic emotional areas seem to be essential for the generation of tinnitus.

Further, abnormal somatosensory afferent input from the neck and face region can affect activity in the central auditory pathways and may also play a role in the generation of tinnitus (Langguth et al. 2013). Approximately two-thirds of tinnitus patients are able to modulate the loudness and pitch of their tinnitus via somatic maneuvers, such as jaw clenching or neck muscles tensing (Roberts et al. 2010).

Somatosensory-auditory interactions (through the ICC) within the central nervous system (brainstem and basal ganglia) are responsible for most of the somatic modulation of tinnitus, including the development of auditory perceptions via somatic testing. In addition to those interactions, muscle spindles may initiate neural activation that finally affects the central auditory pathway, including the dorsal CN (Levine et al. 2003). Some neurons in the non-classical auditory pathways also receive somatosensory input, as mentioned earlier. This finding has also been verified by electrical stimulation of the median nerve at the wrist, which influences the loudness perception of monoaural sounds (Moller & Rollins 2002).

Knowledge of the involvement of neurotransmitter systems in the pathophysiology of tinnitus is rather scarce and predominantly indirect (Langguth et al. 2011). As stated earlier, tinnitus perception takes place in the prefrontal, primary temporal and temporo-parietal associative areas, as well as in the striato-limbic system. Dopamine functions as a neurotransmitter, especially in regard to reward-motivated behavior (for example, many addictive drugs increase dopamine activity), but also in motor control and in controlling the release of various hormones. In addition, dopamine is assumed to regulate auditory processing and gating (Du & Jansen 2011) similar to its role in pain processing (Jääskeläinen et al. 2014). Dopaminergic receptors are located both in the cochlea (Puel 1995) and in the central nervous system structures that are involved in tinnitus (Rauschecker et al. 2010). As tinnitus perception and dopaminergic pathways share the same cerebral structures, which control, e.g., attention, stress, emotions, learning, memory, and motivated behavior, it has been speculated that the dopaminergic system is also involved in tinnitus pathophysiology (Figure 4) (Lopez-Gonzalez & Esteban-Ortega 2005; Langguth et al. 2011). However, this theory has not been verified clinically since neither dopaminergic nor anti-dopaminergic drugs have as yet shown any convincing therapeutic effects on tinnitus (Langguth et al. 2011).

Serotonin is a neurotransmitter that regulates in addition to mood, appetite and sleep, also some cognitive functions, such as memory and learning. Serotonin has been hypothesized as playing a role in tinnitus, especially regarding its comorbidity with depression and insomnia (Rauschecker et al. 2015). In addition, serotonin on the cortical level probably contributes to top-down pain regulation (Martikainen et al. 2018). Anatomical findings imply that serotonergic axons from the dorsal raphe nucleus, the NAc, and other paralimbic regions innervate the thalamic reticular nucleus and the dorsal thalamus (Brown & Molliver 2000). The serotonin hypothesis is supported by the finding that serotonin modulates the loudness dependency of the amplitude of auditory evoked potentials (Juckel et al. 1997) and the observation that serotonin depletion results in a hypersensitivity to noise (Marriage & Barnes 1995). However, serotonin reuptake inhibitors

(antidepressive drugs) that modulate serotonin at the synaptic level for the treatment of tinnitus have only been tested in a few studies, and these have resulted in controversial findings (Langguth et al. 2011).

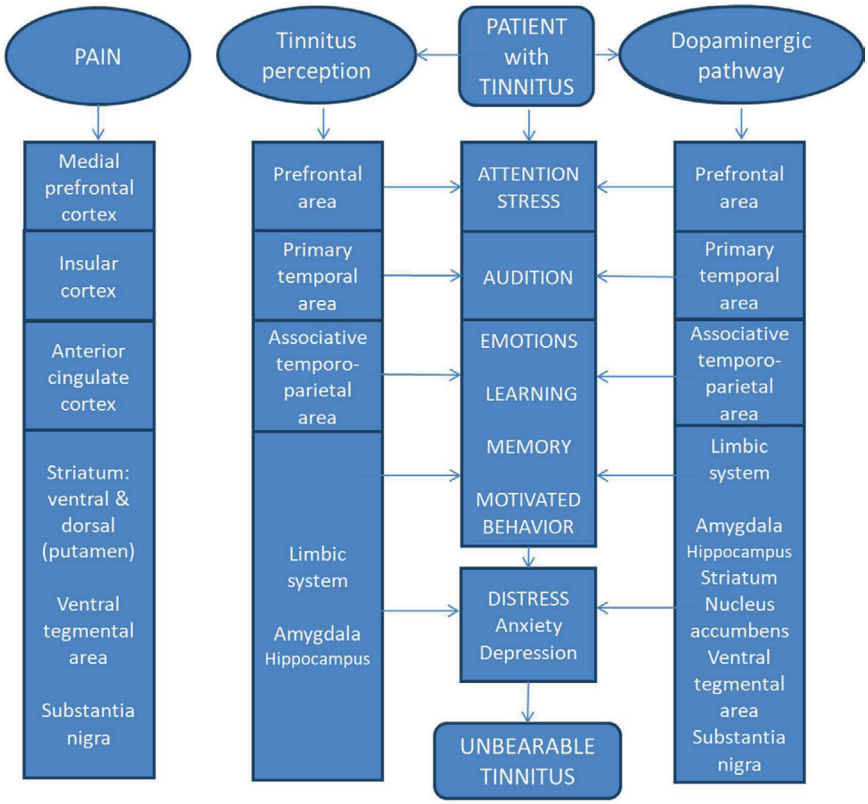


Figure 4. Tinnitus and dopaminergic pathway. Pain cascade is illustrated on the left to show similarities in the brain circuits involved in both conditions. Modified from (Lopez-Gonzalez & Esteban-Ortega 2005).

There is some indirect evidence for the involvement of the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), in tinnitus pathophysiology (Langguth et al. 2011). Salicylate-induced changes in tinnitus seem to be transmitted by the down-regulation of GABAergic cortical inhibition (Sun et al. 2009). $GABA_A$ receptors are involved in intracortical inhibition. Benzodiazepines enhance the effect of the GABA at the $GABA_A$ receptor, resulting in sedative, anxiolytic, and muscle relaxant properties. Further, benzodiazepines have been shown to reduce tinnitus in some patients (Johnson et al. 1993), and tinnitus may

also occur as a withdrawal symptom after prolonged use of benzodiazepines (Busto et al. 1986).

Glutamate serves as a excitatory neurotransmitter and uses the N-methyl-D-aspartate (NMDA) receptors. Glutamate receptors are expressed throughout the auditory pathways (Puel et al. 2002; Martinez-Galan et al. 2010). However, no conclusive clinical evidence exists for a role of the glutamatergic system in tinnitus (Langguth et al. 2011), and clinical trials with glutamate antagonists for tinnitus have demonstrated conflicting results (Zenner et al. 2017).

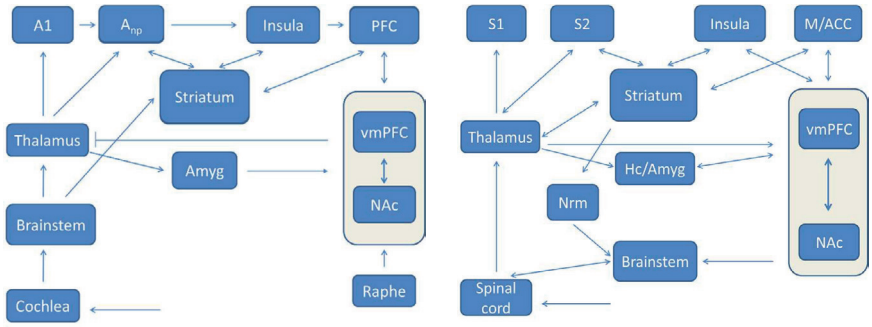
A curiosity, gaze-evoked tinnitus (GET), presents a rare form of tinnitus that may occur after vestibular schwannoma removal. Patients usually describe tinnitus in the deaf ear on the side of the surgery, and the tinnitus can be modulated by a peripheral eye gaze. In functional MRIs of patients with GET, peripheral gaze reduced the cortical inhibition, inhibited the medial geniculate body, and activated the ICC. Additionally, increased tinnitus loudness was represented by increased activity in the CN and the ICC, and reduced intracortical inhibition in the AC (van Gendt et al. 2012).

2.3.2 Primary tinnitus and chronic pain - similarities in the brain network mechanisms

Both chronic tinnitus and neuropathic pain are disabling conditions in which peripheral injury and central deafferentation induce widespread pathophysiological changes in brain function (Rauschecker et al. 2015). Recent studies imply that the higher cognitive and affective brain circuits, including the frontostriatal (Leaver et al. 2011; Rauschecker et al. 2015) and basal ganglia (Jääskeläinen et al. 2014) gating systems, are crucially involved in both disorders. Phantom pain and tinnitus share the same brain networks, as shown previously in Figure 2. The persistence of the phantom perception is based on the memory mechanisms involving the parahippocampal area, amygdala, and hippocampus (De Ridder et al. 2011a). Figure 5 presents the brain structures involved in tinnitus and chronic pain. VmPFC and NAc in the ventral striatum form a frontostriatal gating system for the evaluation and top-down modulation of the sensory stimuli. VmPFC and NAc function together to minimize signals with negative values. Further, different sub-regions of the subcallosal basal ganglia area control tinnitus intensity and distress; vmPFC is part of a positive gain control circuit, and the subcallosal ACC accounts for the negative valuation (Rauschecker et al. 2015; Hagelberg et al. 2004).

If the frontostriatal gating system is compromised, it may affect the perception of the sensory signals in two different ways, i.e., by inducing both a lack of

suppression of irrelevant sensory signals and a dysfunctional valuation process of negative meaning to a neutral stimulus (Leaver et al. 2011; Rauschecker et al. 2010). This process has been suggested to be a learned dysfunctionally reinforced reaction to tinnitus or pain signals (Jastreboff 1990; De Ridder et al. 2011a).



a. b.

Figure 5. The brain structures involved in tinnitus and chronic pain. Block diagrams of relevant brain structures are visualized for tinnitus (a) and chronic pain (b). The diagrams present the most relevant structures and connections, but they are not exhaustive. Abbreviations: A1, Anp, primary and nonprimary auditory cortex; Amyg, amygdala; Hc, hippocampus; M/ACC, mid/anterior cingulate cortex; NAc, nucleus accumbens; PFC, prefrontal cortex; S1, S2, primary and secondary somatosensory cortex; vmPFC: ventromedial prefrontal cortex; Nrm: nucleus raphe magnus. Modified from (Rauschecker et al. 2015).

The frontostriatal gating system is controlled by two major transmitter systems: dopamine and serotonine. As mentioned earlier, it has been speculated that both the dopaminergic and serotonergic systems are involved in tinnitus pathophysiology (Lopez-Gonzalez & Esteban-Ortega 2005; Langguth et al. 2011). Dopamine has also been shown to play a central role in the processing of pain, especially via the striatal dopamine D2 receptors (Hagelberg et al. 2004; Jääskeläinen et al. 2014; Martikainen et al. 2018). Dysregulation in the dopamine signaling system may modulate the experience of pain directly by enhancing the spread of nociceptive signals, and indirectly, by influencing the cognitive processes that affect the experience and interpretation of the nociceptive signals (Jarcho et al. 2012). In addition, the dopamine/dopamine D2 receptor plays a crucial role in gating the multimodal sensory inputs and the attention paid to the salient stimuli. Further, serotonergic modulation has been shown to occur in chronic pain (Rauschecker et al. 2015).

In addition, a reduction in the grey matter volume of the medial prefrontal cortex, as investigated with a voxel-based morphometry, is one of the mutual biomarkers of both tinnitus and chronic pain (Muehlau et al. 2006; Leaver et al. 2011; Smallwood et al. 2013). It is notable though that the exact location of the reduction varies in these different conditions (Rauschecker et al. 2015).

2.3.3 Secondary tinnitus

Secondary tinnitus is caused by a range of auditory and non-auditory system disorders, including a simple cerumen impaction of the external auditory canal; middle ear diseases, such as otosclerosis or Eustachian tube dysfunction; cochlear abnormalities, such as Ménière's disease; and auditory nerve pathology such as acoustic neurinoma. Non-auditory tinnitus can be caused by a wide range of diseases, such as cardiovascular (e.g. hypertension, vascular anomalies), endocrine and metabolic (e.g. diabetes, hypothyroidism), neurological (e.g. migraine, multiple sclerosis, idiopathic intracranial hypertension), and neck or temporomandibular joint disorders. (Baguley et al. 2013; Tunkel et al. 2014)

In some cases, secondary tinnitus can be pulsatile (and objective), synchronous with the heartbeat, as in tinnitus of vascular origin (e.g., arteriovenous fistulas, dural hemangiomas, carotid stenosis or dissecations), or it can be asynchronous as in case of myoclonus of middle-ear or palatal muscles or spontaneous otoacoustic emissions (SOAEs) (Langguth et al. 2013). SOAEs are detected in tinnitus only rarely, and they occur in the same frequency region as the tinnitus, implying a spontaneous activity in the outer hair cells of the cochlea (Kim et al. 2011). However, the role of SOAEs in tinnitus is controversial since SOAEs are usually detected among people without tinnitus.

2.4 Diagnosis of tinnitus and the clinical assessment of tinnitus patients

In most tinnitus patients, no objective test is available (McCombe et al. 2001), so therefore, diagnosis is based on the patient's medical history (somatic/psychiatric disorders, medication, especially ototoxic medications, such as salicylates and aminoglycosides etc.), and an assessment of the tinnitus features and its effects on the patient. Important questions include the onset, duration, location, and characteristics of the tinnitus, especially whether it has a rhythmical or pulsatile component. In addition, it is important to inquire about possible neurological symptoms, such vertigo, difficulties in hearing, and possible noise exposure. (Baguley et al. 2013) Other important questions include what effect the tinnitus

has on sleep, concentration, and mood. Several health questionnaires are available that assess the effects of tinnitus on everyday life, such as the Tinnitus Handicap Inventory (THI) (Newman et al. 1996) consisting of 25 questions with cut-off scores: 0–16 for slight (grade 1), 18–36 for mild (grade 2), 38–56 for moderate (grade 3), 58–76 for severe (grade 4) and 78–100 for catastrophic (grade 5) tinnitus (c.f. Chapter 4.3.1). A faster way to assess tinnitus symptom severity is the Visual Analog Scale (VAS), scoring between 0 (no tinnitus) and 100 (the worst tinnitus the patient could imagine) for self-ratings of tinnitus intensity, annoyance, and distress in everyday life (Adamchic et al. 2012) (c.f. Chapter 4.3.2). Possible concurrent depression can be screened, for example, with the Beck Depression Inventory (BDI) (Steer et al. 1999), which consists of 21 questions with cut-off scores: 0–13 for minimal, 14–19 for mild, 20–28 for moderate and 29–63 for severe depression (c.f. Chapter 4.3.4).

A thorough physical examination is recommended consisting of a complete clinical head and neck examination. It also includes a neurotologic examination, with a complete assessment of cranial nerve function and a careful otomicroscopic examination. If a patient is complaining of pulsatile sound, it is critical to auscultate on multiple locations over the mastoid process, over the carotid arteries and on the ear canal. Pulsatile tinnitus, however, can rarely be objectively detected by auscultation. (Hertzano et al. 2016)

Audiologic testing is recommended to evaluate the type, laterality, and severity of a hearing deficit and determine whether radiographic examinations should be conducted and if any treatment is required for managing the tinnitus or hearing loss (Langguth et al. 2013). In some cases, the clinician can rely on the results of serial audiometric evaluations (presenting only air-conduction thresholds), if there is no/minimal hearing deficit, and hearing is symmetrical. Nevertheless, for an exact diagnosis, an ear-specific pure-tone audiometry with masked air and bone conduction thresholds, (speech recognition threshold (SRT), and word recognition scores) should be conducted. Reliability and validity of these test results should be registered. Air conduction (AC) thresholds are recommended to be measured from 250 to 8000 Hz. Further, if differences in the thresholds at 500 and 1000 or 1000 and 2000 Hertz (Hz) are ≥ a 20 decibel (dB) hearing level (HL), additional mid-octave frequencies at 750, 1500, 3000, and 6000 Hz can be measured. Bone conduction (BC) thresholds are recommended to be measured at 250 to 4000 Hz. (Tunkel et al. 2014) The World Health Organization (WHO) has defined the grades of hearing impairment by the average of pure tone thresholds (PTA) over four frequencies (500, 1000, 2000, and 4000 Hz) of the better ear: 0–25 dB for normal hearing, 26–40 dB for mild, 41–60 dB for moderate, 61–80 for severe and ≥ 81 dB

for profound hearing impairment (WHO Programme for the Prevention of Blindness and Deafness 2006).

As mentioned earlier, cochlear pathology is not always visible in the audiometry of tinnitus patients, but it may be diagnosed with more sensitive audiological measures, like OAE (Mckee & Stephens 1992) or BAEP (Schaette & McAlpine 2011). OAE measures the function of the outer hair cells in the cochlea, and these can be reduced or absent in tinnitus patients. BAEP may show reduced amplitude in tinnitus, especially in the wave I potential, which is generated by primary auditory nerve fibers. In the more central lesions of the auditory pathway, such as acoustic neuronomas, waves II/III – V (generated in the lower pons and inferior colliculus) are abnormal.

Tinnitus can be measured psycho-acoustically with a clinical audiometer to match the pitch (Hz) and loudness (dB) of the tinnitus. However, the results of psycho-acoustic testing of tinnitus perception have been shown to have little, if any, correlation with the degree of tinnitus impact (Henry et al. 2005), and clinically they offer little to the management plan (Baguley et al. 2013). Additionally, tympanometry may be useful for tinnitus patients who are complaining of blocked sensation in the ears so as to evaluate the movements of the tympanic membrane (Langguth et al. 2013).

Patients who have subjective symmetric tinnitus with symmetric sensorineural hearing loss but without any neurological or other significant clinical findings, usually require no further investigations (Hertzano et al. 2016). Patients with asymmetric tinnitus, an asymmetric hearing deficit, or associated neurological focal symptoms or signs will need further radiographic investigation, usually a head MRI (and BAEP) (Tunkel et al. 2014). Patients with a heartbeat-synchronous pulsatile tinnitus need more specific investigations that can include doppler-ultrasonography of the neck vessels, computed tomography (CT), MRI, CT angiography, MRI angiography, or even conventional angiography (Baguley et al. 2013).

2.5 Psychiatric disorders (Axis I) in tinnitus

The International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) is a medical classification created by the WHO (World Health Organization 2016). It is used in Finland, and it contains codes for different diseases, including psychiatric diagnoses. *The Diagnostic and Statistical Manual of Mental Disorders,* 4th Edition (DSM-IV) is published by the American

Psychiatric Association for the classification of mental disorders (American Psychiatric Association 1994). The ICD-10 and the DSM-IV classifications are very much alike, whereas the latest version of the DSM classification, the DSM-5 (American Psychiatric Association 2013) contains extensively revised diagnoses and is not compatible with the ICD-10. Axis I disorders, in the DSM-IV indicate all psychiatric diagnostic categories except for mental retardation and personality disorders. Therefore, Axis I includes psychiatric diagnoses like mood disorders (e.g., dysthymic disorder and major depressive disorder); anxiety disorders (e.g., agoraphobia, social phobia, specific phobia, panic disorder, generalized anxiety disorder and post-traumatic stress disorder); and psychotic disorders.

Structured diagnostic interviews, such as the Structured Clinical Interview for DSM-IV disorders (SCID) (First et al. 1997a) (c.f. Chapter 4.3.8), the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Gülick-Bailer 1995), the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al. 1998), the Composite International Diagnostic Interview (CIDI) (Robins et al. 1988), and the National Institute of Mental Health Diagnostic Interview Schedule (NIMH DIS) (Robins et al. 1981) have been developed for systematic psychiatric diagnostics. The SCID is the most commonly used structured interview worldwide and has a validated Finnish version, whereas no validated versions in Finnish exist for structured interviews based on the ICD-10. Generally, structured diagnostic interviews are suitable for epidemiologic research for coherent diagnostics; however, for very accurate diagnostics, a LEAD system consisting of longitudinal, expert, and all data has been developed (Leckman et al. 1982; Taiminen et al. 2001). The LEAD system includes structured clinical interviews, medical records, and a record of family members, after which the information is integrated and discussed by expert clinicians to form a best-estimate consensus diagnosis. However, it is too time-consuming for diagnostics in larger patient groups.

As stated earlier, the main theories on tinnitus pathophysiology are based on the assumption of a sophisticated interplay between different brain areas, including the limbic system, that creates annoyance and distress to the phantom sound (Langguth et al. 2013). Dopaminergic and serotonergic brain pathways both probably participate in creating a tinnitus sound, as stated earlier (Rauschecker et al. 2015). Also depression has been associated with dopamine and serotonin hypofunction (Lambert et al. 2000; Rauschecker et al. 2015). It thus seems that both tinnitus and depression are pathophysiologically closely interrelated (Langguth et al. 2011). Further, both disorders share symptom overlap, including insomnia, frustration, depressed mood, irritability and concentration difficulties (Tyler & Baker 1983). Clinical experience implies a complex interplay between tinnitus and emotions, as sometimes depressive symptoms will occur as a reaction

to the tinnitus. However, at times, depression may induce decompensation of the existing tinnitus. Further, tinnitus may evolve from a history of an emotional trauma. (Langguth et al. 2011)

Patients with anxiety disorders suffer unnecessary or have disproportional apprehension or fear (American Psychiatric Association 1994). As in depression, it seems that anxiety disorders and tinnitus share several common brain networks, such as the limbic system, which is also a critical functional network in anxiety disorders. Especially, the amygdala is associated with aversive reactions in general, and it plays an important function for threat detection and the emotional processing of fear (Pattyn et al. 2016).

Tinnitus has been associated with psychiatric disorders, especially depression and anxiety, but these reported frequencies vary widely (Pinto et al. 2014; Pattyn et al. 2016). Search of the keywords of "tinnitus" and "psychiatric" discovered there are over 200 articles in the Web of Science. However, most of these studies have used only self-report symptom questionnaires (Geocze et al. 2013; Pinto et al. 2014; Pattyn et al. 2016), such as the BDI (Steer et al. 1999) and the Symptom Check List 90 (SCL-90) (Derogatis 1977), without including any clinical or structured psychiatric diagnostic interview. Such self-report questionnaires are not validated for diagnostic evaluation because they are designed only for screening psychiatric symptoms and for monitoring symptom severity during treatment.

Not surprisingly, the results of the studies using self-report questionnaires have varied widely. Only a few studies have demonstrated a low prevalence rate of depressive symptoms in tinnitus patients, i.e., 8.3% (Figueiredo et al. 2010) with only a weak correlation between tinnitus and depression, and none or minimum depression symptoms for up to 17.2% for those with severe tinnitus (Ooms et al. 2011). However, other studies have reported significantly higher prevalence rates of depressive symptoms, up to 49% (Folmer et al. 2008), and a significant association between depression and tinnitus severity (Folmer et al. 2001; Langguth et al. 2007b). Similarly, most studies investigating tinnitus and anxiety have applied only self-report questionnaires without any structured diagnostic interviews (Pattyn et al. 2016). The difference in methods is essential, since the detection of psychiatric symptoms using self-report scales does not automatically mean that the diagnostic criteria for a psychiatric disorder are fulfilled. Further, for example, depressive symptoms may be indicative of a depressive disorder, but the same symptoms can also occur in many other psychiatric disorders, such as personality disorders, anxiety disorders, bipolar disorder, dementia, or even addiction (Langguth et al. 2011).

There appears to be only 11 studies published in English (Belli et al. 2008; Harrop-Griffiths et al. 1987; Holgers et al. 2005; Malakouti et al. 2011; Marciano et al. 2003; Shargorodsky et al. 2010; Simpson et al. 1988; Sullivan et al. 1988; Zirke et al. 2013; Zöger et al. 2001; Zöger et al. 2006) that have examined Axis I psychiatric disorders in tinnitus patients using a structured diagnostic interview (Table 1). Their findings indicate that 60–78% of tinnitus patients have at least one lifetime psychiatric disorder (Malakouti et al. 2011; Zöger et al. 2001); 32.5–77.5% have a lifetime depression (Malakouti et al. 2011; Sullivan et al. 1988), and about 45% have a lifetime anxiety disorder (Holgers et al. 2005; Malakouti et al. 2011; Zöger et al. 2001) (Table 1). It appears that dissociative disorders have not systemically been studied in tinnitus patients. In the existing literature, the temporal relationships of psychiatric disorders and the occurrence of tinnitus is very seldom reported, and therefore, no conclusions can be drawn for whether tinnitus exposes one to psychiatric disorders or vice versa or whether the two are just comorbid conditions.

2.6 Personality disorders (Axis II) in tinnitus

Axis II disorders in DSM-IV (American Psychiatric Association 1994) indicate the presence of personality disorders and intellectual disabilities. Personality disorders are divided into three clusters; A represents odd and eccentric: paranoid, schizoid, schizotypal personalities; B represents dramatic, erratic or emotional: antisocial, borderline, histrionic, narcissistic; C represents fearful and neurotic: avoidant, dependent, obsessive–compulsive, and additionally there are others: depressive, passive–aggressive and self-defeating. Personality disorders can be reliably diagnosed using a validated diagnostic interview, such as the SCID-II interview (First et al. 1997b) and the International Personality Disorder Examination (IPDE) (Loranger et al. 1994).

The association between tinnitus and personality disorders has not been extensively studied. It appears that only two studies have investigated the prevalence of personality disorders (PD) in tinnitus patients by using a validated diagnostic interview (SCID-II) **(**Table 1**)**. Those studies have demonstrated incongruent rates of 3% (Belli et al. 2008) and 50% (Erlandsson & Persson 2006). Thus, no conclusion can be made for whether the rate of PDs in chronic tinnitus actually differs from the estimates of a 9% prevalence rate of PDs in general population studies (Lenzenweger et al. 2007). Self-report questionnaires are not designed for diagnostic use, but these have similarly revealed differing rates of PDs in tinnitus patients, ranging from 19% (Marciano et al. 2003) to 61% (Zöger et al. 2001). These vastly ranging values suggest either methodological faults in

Table 1. Summary of the studies published in English that have investigated psychiatric disorders in tinnitus patients using a structured diagnostic interview. N/A not applicable. SCID=Structured Clinical Interview for DSM-III/IV disorders, NIMH DIS=National Institute of Mental Health Diagnostic Interview Schedule, MINI=Mini International Neuropsychiatric Interview, CIDI=Composite International Diagnostic Interview, PD=personality disorder, O-CPD=obsessive-compulsive personality disorder
Modified from (Sahlsten et al. 2018).

Authors and year								
Axis I psychiatric disorders	**Sample**	**Instrument**	**Any lifetime axis I disorder (%)**	**Lifetime depression (%)**	**Lifetime anxiety (%)**	**Any current axis I disorder (%)**	**Current depression (%)**	**Current anxiety (%)**
Belli et al 2008	90	SCID-I	N/A	N/A	N/A	24.4	7.8	27.8
Harrop-Griffiths et al 1987	21	NIMH DIS	N/A	61.9[B]	N/A	N/A	47.6[E]	28.6
Holgers at al 2005[1]	127 (82)	SCID-P	76.8	61.0	45.1	65.9	39.0	45.1
Malakouti et al 2011	400	SCID-I	60.0	32.5[B]	45.8	55.2	N/A	N/A
Marciano et al 2003[2]	75	MINI	N/A	N/A	N/A	77.3	N/A	29.3
Shargorodsky et al 2010[3]	2265	CIDI	N/A	N/A	N/A	N/A	N/A	N/A
Simpson et al 1988	24	SCID	N/A	N/A	N/A	62.5	54.2	29.2
Sullivan et al 1988	40	NIMH DIS	N/A	77.5[B]	N/A	N/A	60.0[E]	N/A
Zirke et al 2013[4]	100	CIDI	N/A	N/A	N/A	46.0	N/A	32.0
Zöger et al 2001[5]	82	SCID-P	78.0	62.2	45.1	54.9	39.0	45.1
Zöger et al 2006[6]	224 (80/144)	SCID-P	N/A	N/A	N/A	46/81	33[E]/52[E]	45/49
Axis II psychiatric disorders	**Sample**	**Instrument**	**Any PD (%)**	**Any cluster A PD (%)**	**Any cluster B PD (%)**	**Any cluster C PD (%)**	**O-CPD (%)**	**Avoidant PD (%)**
Belli et al 2008	90	SCID-II	3.3	0	1.1	3.3	1.1	2.2
Erlandsson&Persson 2006[7]	70 (18)	SCID-II	50.0	0	38.9	27.8	16.7	11.1

[1] SCID-P was conducted on 82 patients. [2] Affective disorders were analyzed (27%), but depression was not separately. Personality disorders were not analyzed using a diagnostic interview. [3] Only major depression (9.3%) and generalized anxiety disorder (20.4%) were analyzed using CIDI with no division for lifetime or current. [4] Affective disorders were analyzed (37%), but depression not separately. [5] Personality traits were also evaluated. [6] 80 consecutive and 144 high-risk tinnitus patients were evaluated. [7] SCID-II was conducted only on a sub-group of 18 patients. The majority of patients had a comorbidity of personality disorders. [B] The rate of lifetime major depression, [E] The rate of current major depression

the evaluation of PD, very variable patient samples, or large effects of cultural factors. PDs can cause a significant handicap in functioning and are usually comorbid with other mental disorders, and further, patients with PD are typically frequent users of health services (Lenzenweger et al. 2007).

2.7 Treatment of tinnitus

2.7.1 General aspects

Treatment of tinnitus is challenging since these patients often hope that the phantom sound can be totally removed. No curative therapy for primary tinnitus exists, although almost 60 different treatment modalities have been reported (Zenner et al. 2017). The current treatment strategies aim at improving the patient's ability to cope with the symptoms. The most efficient treatment seems to be enhancing the habituation to tinnitus sound by counselling and enrichment of the sound enviroment. Treatment of comorbid depression, anxiety and sleep disturbancies can improve the quality of life. Management of secondary tinnitus is naturally targeted toward the identification and treatment of the specific underlying condition, and thus, this tinnitus may be curable (Eisenman & Teplitzky 2016; Tunkel et al. 2014).

First of all, clinicians should distinguish between those patients with bothersome tinnitus and patients with non-bothersome tinnitus by discussing the sitution with the patient and, if needed, using inventories. Bothersome tinnitus causes distress for patients and affects their quality of life and functional health state, and these patients desire treatment to alleviate their tinnitus. On the contrary, non-bothersome tinnitus does not have a significant effect on the quality of life, but it may result in some curiosity or concern about the etiology, the natural history of the condition, and the different treatment options. It is important to separate these two patient groups precisely to avoid unnecessary interventions for those who neither need nor want them. (Tunkel et al. 2014)

Throughout the tinnitus literature, patient counselling is highly recommended and should be part of the treatment for every tinnitus patient (Baguley et al. 2013; Langguth et al. 2013; Tunkel et al. 2014; Zenner et al. 2017). Counselling should consist of general information on tinnitus, including the association between tinnitus and a hearing deficit, and discussion of lifestyle factors that can have either positive or negative effect (like noise exposure or stress) on the tinnitus. For the patients, it is important to know that there is nothing dangerous behind the tinnitus sound and that it is rather a benign symptom that the nervous system creates because of a hearing deficit. Counselling should give these patients advice (like

enrichment of the sound environment) and more empowerment to help achieving habituation and better coping with emotional stress, sleep difficulties and attention problems. Additionally, information on different treatment modalities, including tinnitus groups and self-treatment options (e.g., books, sound therapy with everyday devices, such as a Smartphone), should be offered. The effectiveness of counselling has only been assessed, together with other interventions, such as retraining (Jastreboff 1990) and cognitive behavioural therapy (Zenner et al. 2013). No study has systematically compared the various forms of counselling (Zenner et al. 2017), and the efficacy of self-help interventions has not been properly studied (Greenwell et al. 2016).

2.7.2 Hearing aids and psychological or sound therapies

Hearing rehabilitation with a hearing aid is recommended for those patients with hearing loss and bothersome tinnitus (Tunkel et al. 2014). This recommendation is mainly based on observational studies that have provided only a moderate or weak evidence base (Hoare et al. 2014; Searchfield et al. 2010). However, the clinical experience indicates that the use of hearing aids for tinnitus provides benefits by making the patient less aware of the tinnitus. The sound environment is enriched, and improved communication is achieved with an amplification of the sounds in a certain frequency zone, as needed (Del Bo & Ambrosetti 2007). For the best results, hearing aids should be fitted to both ears. Profound hearing loss or deafness is an indicator for a cochlear implant (CI), and CIs have usually reduced tinnitus in these particular patients (Baguley & Atlas 2007; Blasco & Redleaf 2014). However, rarely an induction of (temporary or permanent) tinnitus has also been reported after CIs (Ramakers et al. 2017).

Sound therapy for tinnitus is based on using any sound with the intent of changing the tinnitus perception or reactions to tinnitus to thereby gain clinical benefit. It is used for tinnitus treatment although the evidence of its effects on tinnitus is rather weak (Hobson et al. 2012; Zenner et al. 2017). Sound therapy aims to create relief from the tinnitus stress by reducing the contrast between the environment and the patient's perception of the tinnitus, and also by distracting the patient's attention from the tinnitus (Tunkel et al. 2014). Different acoustic devices are used, including environmental enrichment devices, sound generators, combination tinnitus instruments (a sound generator and a hearing aid in the same unit), and conventional hearing aids.

A standardized method for the treatment of tinnitus, Tinnitus Retraining Therapy (TRT) was created based on the neurophysiological model of tinnitus (Figure 3) (Jastreboff & Hazell 1999). It uses a combination of educative counselling and sound therapy in a strict framework to reduce or remove the aversive reaction to

the tinnitus. The main goal of TRT is to reclassify tinnitus into a ranking of a neutral stimulus, while the main goal of sound therapy is to reduce the tinnitus-related neuronal activity. TRT and its modifications are one of the most commonly used treatment options for tinnitus. Any type of tinnitus, including somatosounds, may be treated using TRT, because the treatment operates above the tinnitus source, and at those connections that link the auditory and other systems in the brain.

Phillips and McFerran (2010) conducted a systematic review to evaluate the efficacy of TRT, including trials that compared TRT with either no treatment or other forms of tinnitus therapy (Phillips & McFerran 2010). Most studies were excluded because they used modified versions of the TRT protocol, and only one trial (Henry et al. 2006) was included. They concluded that TRT is much more effective for tinnitus patients than tinnitus masking alone. Generally, over 100 publications on TRT or its modifications have been published, and most suggest that TRT offers significant help for about 80% of patients (Jastreboff 2015).

Cognitive behavioral therapy (CBT), originally developed for the treatment of depression and anxiety, is recommended for the treatment of persistent, bothersome tinnitus (Tunkel et al. 2014). CBT uses relaxation, cognitive restructuring of the thoughts, and exposure to exacerbating situations to promote habituation. In the therapy, skills are teached to identify negative thoughts that result in distress, and these are restructured into thoughts that are more accurate or helpful. Additionally, instructions on sleep hygiene and auditory enrichment are given. CBT can be applied to individuals or to a group. Most studies of CBT for tinnitus involve 8 to 24 weekly sessions, each lasting from 60 to 120 minutes (Hesser et al. 2011).

CBT has been used to treat tinnitus for over three decades, and it is the best investigated psychotherapeutic strategy for coping with tinnitus (Langguth et al. 2013). Benefits persist for 12 months or longer, in fact, one study reported even a 15-year stability in the improvement after the completion of CBT (Goebel et al. 2006). In a meta-analysis of 15 randomized controlled trials (RCTs), CBT was shown to be effective for the treatment of tinnitus distress (Hesser et al. 2011). A Cochrane review (2010) using 8 trials concluded that CBT offers a significant improvement in the depression associated with tinnitus in 6 trials, and a decrease of global tinnitus severity in 5 trials, but it did not find any effect on subjective tinnitus loudness in 6 trials (Martinez-Devesa et al. 2010).

2.7.3 Medical therapy

Thus far, no medications have been shown to reliably cure or reduce primary tinnitus. The U.S. clinical practice guidelines for the treatment of tinnitus (2014) recommend against routine use of antidepressants, anticonvulsants, anxiolytics, or intratympanic medications for a primary indicator for treating persistent, bothersome tinnitus (Tunkel et al. 2014).

A Cochrane review (2012) of antidepressants for patients with tinnitus concluded there is no sufficient evidence of antidepressant drug therapy improving tinnitus (Baldo et al. 2012). In this review, 6 trials had generally low quality (methodological concerns of dosing issues, failure to use validated tinnitus questionnaires, and small study groups); 4 of these investigated the effect of tricyclic antidepressants on tinnitus, one trial investigated the effect of a selective serotonin reuptake inhibitor (SSRI), and one investigated trazodone, an atypical antidepressant, on tinnitus. All the trials that examined tricyclic antidepressants implied that there was a slight improvement in tinnitus, but these treatment effects may have been related to a modulation of depression and anxiety rather than any real change in the tinnitus. The trial that investigated the SSRI drug (paroxetine) concluded that the majority of the tinnitus patients did not benefit from paroxetine in a consistent fashion (Robinson et al. 2005). However, the research did recommend further studies to determine if any subgroups of patients, like depressed tinnitus patients and those patients who tolerated higher doses of this medication, could benefit. In the trial that investigated trazodone, the results indicated an improvement in tinnitus intensity and quality of life after treatment, but there was no significant difference between the drug and the placebo groups (Dib et al. 2007). In conclusion, although antidepressants may not improve tinnitus, they can improve depression and anxiety in tinnitus patients, and thus, they can improve the quality of life in those particular patients (Savage & Waddell 2014).

Anticonvulsants are not recommended for tinnitus treatment (Tunkel et al. 2014). They have been experimented for use with tinnitus based on the belief of their ability to reduce tinnitus by augmenting the action or levels of neurotransmitters (gamma-aminobutyric acid [GABA], glutamate) or via the inhibition of cell depolarization by blocking sodium channels (Hoekstra et al. 2011). A Cochrane review of 7 placebo-controlled trials of anticonvulsants (gabapentin, carbamazepine, lamotrigine, or flunarizine) for chronic tinnitus found no evidence that anticonvulsants had any clinically meaningful positive effect in the treatment of tinnitus; however, a small effect with doubtful clinical significance was demonstrated (Hoekstra et al. 2011). Further, carbamazepine has been associated with adverse effects, such as dizziness, nausea, and headache, and thus, it is

classified as likely to be ineffective or even harmful for tinnitus patients (Savage & Waddell 2014). Subsequent to the Cochrane review, a randomized placebo-controlled trial of an 8-week treatment with gabapentin in an escalating dosing scale was published (Dehkordi et al. 2011). It interestingly concluded that although there was no significant difference between gabapentin and the placebo groups, patients with concomitant hypertension, diabetes, or dyslipidemia could benefit from gabapentin.

Clinical trials using anxiolytics, such as benzodiazepines, for tinnitus do not consistently show benefit, and therefore, their routine use is not recommended. Further, these medications can have adverse effects, like dependence and memory deficits from long-term use, unless dosing is meticulously monitored and carefully tailored along with drug-free periods (Langguth et al. 2013). A double-blind, placebo-controlled study of 40 patients that investigated alprazolam showed reduced tinnitus loudness in 76% of the patients based on tinnitus matching and a visual analogue scale (VAS) (Johnson et al. 1993). Nevertheless, another study of alprazolam in 36 patients in a triple-blind randomized crossover design, using an active control, chlorpheniramine, to simulate the effect of drowsiness, did not find any difference in the THI scores or tinnitus loudness. However, they did discover a significant improvement in the VAS scores for tinnitus severity (Jalali et al. 2009). A systematic review analyzed 6 studies using benzodiazepine for tinnitus; clonazepam was found to be effective in three studies (but they all had limitations in adequate blinding). The effectiveness of alprazolam was equivocal, and diazepam was not effective in two studies, while oxazepam was effective in one study (Jufas & Wood 2015). They concluded that no robust evidence base exists for benzodiazepine use in subjective tinnitus, and clonazepam offers the most evidence to support its use (Bahmad et al. 2006; Han et al. 2012) although caution is needed, given its side effects.

Four glutamate antagonists, applied as off-label medications, have been used in clinical trials for tinnitus patients: Acamprosite/acamprosate, memantine, neramexane, and caroverine, as reviewed by Zenner et al (2017). Only studies investigating acamprosate, a medication used to treat alcohol dependence, found significant improvement in tinnitus (de Azevedo & Figueiredo 2007; Sharma et al. 2012). Acamprosate acts both as a glutamate antagonist and a GABA agonist. However, the results of these two studies cannot be considered as adequate evidence of efficacy due to the low methodological quality and insufficient patient samples (Zenner et al. 2017).

Neither dopaminergic nor anti-dopaminergic drugs have shown convincing therapeutic effects on tinnitus (Langguth et al. 2011). An RCT of 100 patients investigated a dopamine agonist, piribedil, for the treatment of chronic tinnitus,

and it found that piribedil was not superior to the placebo (de Azevedo et al. 2009). Further, an RCT of 40 tinnitus patients investigated pramipexole, an agonist on D2/D3 receptors, and concluded that pramipexole was an effective agent against subjective tinnitus associated with presbyacusis (Sziklai et al. 2011); pramipexole attained a significant improvement of tinnitus in 35% of patients (measured with THI and tinnitus match), and in addition, produced complete tinnitus cessation in 5 patients. However, only 20 patients were treated with pramipexole with a follow-up of only 4 weeks, so further studies are needed to confirm these results.

Controlled trials on systemic steroids for the treatment of chronic tinnitus have not been published (Zenner et al. 2017), although steroids are successfully used after acute acoustic trauma, resulting in better hearing outcomes (and thus less tinnitus) (Le et al. 2017), and also in sudden sensorineural hearing loss, although with contradictory evidence (Crane et al. 2015). Some RCTs have investigated intratympanically applied corticosteroids for tinnitus patients, but without any significant effects (Araujo et al. 2005; Topak et al. 2009; Choi et al. 2013). Of these studies, Topak et al (2009) had the largest patient sample at 70 patients in a placebo-controlled trial that investigated intratympanic injection of either methylprednisolone or saline. They concluded that the severity of the tinnitus distress did not change significantly in either group.

The local anaesthetic, voltage-gated, sodium channel blocker, lidocaine, has led to a transient suppression of tinnitus in some patients after intravenous application (Weinmeister 2000; Baguley et al. 2005). The action sites in tinnitus suppression are both in the cochlea and the central auditory nervous system (Trellakis et al. 2007). However, intravenous injection of a local anaesthetic has too many risks for routine therapeutic use in tinnitus (Baguley et al. 2013). Alleviation of tinnitus with the intratympanic use of lidocaine has not been proven, and it also carries side effects like vertigo and vomiting (Coles et al. 1992; Podoshin et al. 1992). Nevertheless, one study of 40 patients investigating intratympanic lidocaine and dexamethasone injections (ITLD) compared to a control (saline) for idiopathic tinnitus with a 6-month follow-up concluded that there were significant differences between the groups (measured with an improvement in the tinnitus questionnaire by a decrease ≥ 2 items, in the THI a decrease of ≥ 5 or in a >5 dB in tinnitus loudness matching). ITLD seemed to be effective for tinnitus (Elzayat et al. 2016). At 6 months, the improvement rates in the tinnitus questionnaire, the THI, and the loudness matching test were 78.5% in all tests in the ITLD group, compared to 40.0, 40.0 and 30.0% in the saline group. Further, local lidocain injections on the cervical and upper thoracic area muscle trigger points have also been experimented with as tinnitus treatment. The treatment effects are mostly temporary and partial,

but in one study, more than one third benefitted from it compared to the untreated control patients also with tinnitus (Estola-Partanen 2000).

Melatonin, a hormone secreted by the pineal gland, is not recommended for the routine treatment of tinnitus (Tunkel et al. 2014), but it may be useful for tinnitus patients with sleep disturbance (Megwalu et al. 2006). Some studies on the topic have demonstrated a benefit especially in patients with severe tinnitus and insomnia (Rosenberg et al. 1998; Hurtuk et al. 2011; Megwalu et al. 2006). However, these results should be interpreted cautiously because of small patient samples and certain methodological limitations, including lack of a placebo group in one of the trials (Megwalu et al. 2006; Tunkel et al. 2014).

Medications aimed at improving microcirculation in both the central and peripheral auditory systems have also been assessed in tinnitus treatment (Baguley et al. 2013), including diuretics (Mulders, Wilhelmina H A M et al. 2014), anticoagulants (Mora et al. 2003) and vasodilators (Davies et al. 1994), but without any essential success. Betahistine is supposed to alleviate Ménière's disease by improving cochlear blood flow. However, no available substantial evidence implies that betahistine is effective in the tinnitus from Ménière's disease or in other types of tinnitus (James & Burton 2001).

Botulinum toxin has successfully been used to treat objective tinnitus, including idiopathic muscular tremor in the soft palate and the essential palatal tremor (Slengerik-Hansen & Ovesen 2016). However, the evidence for using botulinum toxin in the treatment of subjective tinnitus is still insufficient (Lainez & Piera 2007; Zenner et al. 2017).

2.7.4 Other treatments

Hyperbaric oxygen has been commonly used in the treatment of hearing loss following acoustic trauma (Salihoglu et al. 2015), but its benefit when treating chronic tinnitus has not been proven (Zenner et al. 2017). A Cochrane review (2012) on hyperbaric oxygen for idiopathic, sudden sensorineural hearing loss and tinnitus evaluated 7 trials with 392 patients (Bennett et al. 2012). These trials proved to be small and generally of poor quality. The review concluded that hyperbaric oxygen significantly improved hearing in sudden hearing loss, but the clinical significance remained unclear. No evidence of any beneficial effect of hyperbaric oxygen on chronic hearing loss or chronic tinnitus was found. In addition, physicians should be aware of both middle and inner ear barotrauma as potential complications of this treatment (Yamamoto et al. 2016).

Low-level or soft laser therapy has been used for some chronic pain treatment, although the exact mechanisms of its action remain unclear. The therapy may enhance local blood flow in the inner ear or activate repair mechanisms by photophysically stimulating the mitochondria in the hair cells. Based on the similarities between chronic pain and tinnitus, lasers have been commercially manufactured for use in tinnitus, though no specific mechanisms of action are known. Although the results of a few studies have suggested some efficacy for laser therapy in tinnitus, most imply that it is ineffective (Baguley et al. 2013; Gungor et al. 2008). The effectiveness of laser therapy for alleviating tinnitus has also varied widely with the reported success rates ranging between 0% and 80% (Dehkordi et al. 2015). In recent RCTs, transmeatal laser was no more effective than the placebo for subjective tinnitus (Ngao et al. 2014; Dehkordi et al. 2015). However, laser treatment may be helpful for those tinnitus patients with temporomandibular disorders (Demirkol et al. 2017).

The most commonly used herbal supplement for tinnitus is ginkgo biloba (or ginkgo biloba extract, EGb 761), but it is not recommended, given the weak evidence base (Tunkel et al. 2014). A Cohrane review (2013) evaluated 4 RCTs of 1543 patients on the efficacy of ginkgo biloba and found no evidence of efficacy (Hilton et al. 2013). Further, side effects, such as dizziness, stomach upset, allergic reactions and a tendency to bleed, were reported (Roland & Nergrd 2012). Ginkgo biloba may also inhibit hepatic cytochrome P450, and thus, affect the metabolism of its substrates.

Zinc is an essential trace element found in living cells and fluids throughout the body, and it has been assessed for tinnitus treatment (Tunkel et al. 2014). Its proposed mechanisms of action in tinnitus control involve wide distribution in the central nervous system, including the auditory pathway, an essential role in protection against reactive oxygen species, and a possible effect on depression (Speich et al. 2001; Coelho et al. 2007). Prevalence rates of zinc deficiency in patients with tinnitus range from 2% to 69%, with older patients affected more frequently (Coelho et al. 2007). Zinc supplements may reduce tinnitus in patients with zinc deficiency (Arda et al. 2003), but in RCTs, zinc has not been shown to be effective for tinnitus overall (Paaske et al. 1991; Coelho et al. 2013).

Several other dietary supplements or antioxidants have been used to treat tinnitus, including lipoflavonoids, garlic, homeopathy, traditional Chinese/Korean herbal medicine, honeybee larvae, and various vitamins/minerals (Tunkel et al. 2014). No dietary supplement has ever been approved for the treatment of tinnitus, and none has been shown to cure tinnitus. Further still, dietary supplements can cause side effects or interactions, especially when taken along with conventional medications.

Unconventional treatment methods for tinnitus include (electro)acupuncture and hypnosis. No convincing evidence of efficacy exists for either one (Kim et al. 2012; He et al. 2016; Savage & Waddell 2014).

Electromagnetic techniques, both non-invasive and invasive, for tinnitus treatment are described in Chapters 2.8 and 2.9. Generally, patients and clinicians should be cautious when considering invasive or potentially harmful experimental managements for tinnitus, since tinnitus is not a life-threatening condition (Folmer et al. 2014). Additionally, if some advancement is achieved from medically or genetically (like gene or stem cell therapy) treating a sensorineural hearing deficit, that progress could also help simultaneously reduce tinnitus in many patients.

2.8 Transcranial magnetic stimulation (TMS)

2.8.1 Transcranial magnetic stimulation (TMS) of the brain – technical background and its mechanisms of action

Transcranial magnetic stimulation (TMS) is a non-invasive method, in which magnetic pulses are applied to the scalp with a special coil. Magnetic pulses induce an electric field onto the brain causing activation or inactivation of the neural networks (Lefaucheur et al. 2014). Already in 1831, Michael Faraday stated in his law that a time-varying electric current creates an orthogonal magnetic field, which can induce an electric field, and therefore, a secondary current within a nearby conducting medium. In the 1980s, the first magnetic stimulator was designed to stimulate the brain transcranially (Barker & Jalinous 1985), and in the 1990s, TMS reached clinical use (Barker 1999). Several TMS techniques today are found in routine diagnostic or therapeutic use (Rossi et al. 2009).

The TMS equipment includes a high current pulse generator for producing a discharge current of several thousand amperes that then flows through a stimulating coil, generating a brief magnetic pulse with field strengths up to several Teslas (normally approximately 2.0 T) (Lefaucheur et al. 2014). When a coil is placed on the head, the magnetic field undergoes only a little attenuation by the extracerebral tissues, and thus, it is able to induce an electric field sufficient to depolarize the cortical neurons and axons of the pyramidal cells and activate the neural networks of the brain. This electric field can reach up to 150-180 V/m in the cortex (Massimini et al. 2007) and is able to activate cortical neurons at a depth of 1.5-3.0 cm beneath the scalp (Rossi et al. 2009). The direction of the induced electric current is opposite to the direction of the current in the coil (Kammer et al. 2001). When TMS pulses are applied repetitively (rTMS), they can modulate

cortical excitability, increasing or decreasing it via LTP (long-term potentiation) or LTD (long-term depression)-like mechanisms that either enhance or inhibit synaptic transmission within the stimulated neural network (Hoogendam et al. 2010). The effects of rTMS last from days to months, but are not permanent. The postsynaptic NMDA receptor seems to modulate the LTP and LTD effects, as in an experimental settings, the stimulation effects can be prevented by the application of a NMDA receptor antagonist (Dudek & Bear 1992). Further, LTP and LTD strongly depend on the activation of dopamine receptors, as dopamine probably exerts a slow modulation of synaptic transmission, thus either inhibiting or enhacing the neuronal activity. The LTP and LTD are lost after the pharmacological or genetic disruption of the dopamine mediated pathway (Calabresi et al. 2007).

The current density generated into the brain depends on many variables, including the type and the orientation of the coil, the distance between the coil and the brain, as well as on the magnetic pulse waveform, and the intensity, frequency and pattern of the stimulation. Large "circular" coils have a wide action radius. Focusing is better with a "figure-of-eight" coil, the stimulation zone being but a few square centimeters and rather shallow (Thielscher & Kammer 2004), whereas the double-cone coil is designed for deeper cortical stimulation (Roth et al. 2002). Monophasic magnetic pulses are commonly used only for single-pulse experiments. In rTMS, biphasic pulses are usually used because of the lower stimulation threshold and less heating of the coil required (Sommer et al. 2006). Usually the coil is oriented perpendicular to the stimulated brain gyrus for optimal stimulation (Di Lazzaro et al. 2003).

RTMS treatment can be targeted by positioning the coil according to external anatomical landmarks or EEG 10/20 electrode locations. These non-navigated "blind" or "standard" methods have been shown to be fairly inaccurate (by 1–2 cm) to the anatomical cortical targets actually stimulated (Ahdab et al. 2010). RTMS can be navigated over hyper/hypometabolic or hyper/hypoactive cortical regions, as detected by positron emission tomography (PET), functional magnetic resonance imaging (fMRI) or they can be based on a structural MRI (Langguth et al. 2010). Neuronavigation enables more precise definition of the stimulation target and better reproducibility of the stimulation (Fitzgerald et al. 2009; Ayache et al. 2016).

Most of the data on TMS effects have been derived from the stimulation of the precentral region (M1) in healthy subjects to obtain motor evoked potentials (MEPs). The size of these MEPs reflects the excitability of motor corticospinal output (Lefaucheur et al. 2014). Low frequency (LF) (≤ 1 Hz) rTMS has been shown to decrease cortical excitability, both in experimental settings and in

humans, while high frequency (HF) (> 5 Hz) stimulation is excitatory (Siebner & Rothwell 2003; Plewnia et al. 2007). However, some studies have implied that both LF and HF stimulations may have mixed excitatory and inhibitory effects depending on the stimulation intensity, the target, and the length of the stimulation time (Houdayer et al. 2008; Gamboa et al. 2010). For example, doubling the duration of the stimulation can reverse the outcome from inhibition to excitation and vice versa (Gamboa et al. 2010).

Further, the excitatory and inhibitory effects of rTMS may also depend on individual differences in the baseline cortical excitability (Siebner & Rothwell 2003; Daskalakis et al. 2006), and the interneuron networks recruited by TMS (Di Lazzaro et al. 2011; Hamada et al. 2013). Therefore, rapidly changing excitability states in an oscillating brain neuronal network may influence rTMS efficacy. Applying the rTMS pulses with EEG control syncronously to the background brain oscillations, utilizing so called closed-loop TMS-EEG, may be more efficient to induce plasticity in the targeted neuronal networks (Zrenner et al. 2018). Additionally, the excitatory and inhibitory aspects of rTMS may depend on the activity level of GABAergic system: for example, a MEP increase after HF rTMS may be the result of a decrease of GABA-mediated intracortical inhibition, rather than a direct increase of motor cortex excitability (Ziemann 2004). Besides GABA, the glutamatergic system also contributes, as LF rTMS on the AC has been shown to down-regulate glutamate signalling (Cacace et al. 2017).

Additionally, rTMS may affect the spontaneous oscillatory rhythms of the cortical brain circuits (Houze et al. 2013). Various brain disorders, like tinnitus (Mueller et al. 2013), Parkinson's disease (Brown 2006) and schizophrenia (Barr et al. 2011; Canali et al. 2015) have pathological oscillatory rhythms between the cortical and deep brain structures. For example, in schizophrenia, 20 Hz rTMS has been demonstrated to decrease the excessive gamma oscillation (30–50 Hz) typical to this condition (Barr et al. 2011). In tinnitus, a reduction of the inhibitory idling alpha band rhytm (8–12 Hz) in the AC has also been demonstrated (Weisz et al. 2005). Further, LF rTMS has been shown to increase the alpha power in the stimulated AC, which is associated with a reduction in tinnitus loudness (Mueller et al. 2013). Therefore, the therapeutic effects of rTMS may partly be due to the modulation of oscillations in the neural networks and the restoration of intracortical inhibitory circuits (Fuggetta & Noh 2013).

In addition to activating the local neural circuits, rTMS can activate neural networks thereby projecting to distant structures (Fox et al. 1997; Di Lazzaro et al. 2011; Lefaucheur 2012; To et al. 2018), even to the contralateral hemisphere and cerebellum (Okabe et al. 2003). This activation has been shown both by functional imaging studies (Bestmann et al. 2005; Siebner et al. 2009; Lee et al. 2013) and

functional connectivity studies (Munchau et al. 2002; Rizzo et al. 2004). Further, rTMS can modulate the neurotransmitter system even in deep brain areas, especially by increasing dopamine release in basal ganglia (Strafella et al. 2001; Keck et al. 2002). RTMS has also been shown to activate the endogenous opioid system in a widely distributed brain network in humans (Lamusuo et al. 2017). The release of serotonin by rTMS has been clearly demonstrated in an experimental animal study (Viisanen & Pertovaara 2010).

Irrespective of the indication, rTMS treatment effects seem to vary widely between patients, as do the effects of the more invasive, intracranial neuromodulatory treatments. Both rTMS and invasive neuromodulation techniques have shown response rates ranging from 50% to 70%; some patients do not benefit from the neuromodulation treatments at all (Lefaucheur et al. 2014). In addition to TMS techniques, protocols, and stimulation targets, the level of individual cortical excitability at the baseline is an important source for inter-individual diversity of rTMS effects (Siebner & Rothwell 2003). This could be one reason why rTMS effects on intracortical inhibition depend more on baseline individual values than on stimulation frequency (Daskalakis et al. 2006). Generally, previous neuronal activity modulates the capacity for subsequent plastic changes (Turrigiano & Nelson 2004). Further, medication, age, gender, and especially genetic factors can modify the effects of rTMS (Lefaucheur et al. 2014). Central nervous system medications can influence rTMS efficacy, for example, by decreasing MEP amplitude, as $GABA_A$ receptor agonists, benzodiazepines, and barbiturates (Ziemann 2004).

Genetic differences contribute to the individual ability of LTP- and LTD-like synaptic events produced by rTMS forming one source of variation in the therapeutic responses (Hoogendam et al. 2010). Two genetic polymorphisms have been indicated to influence the rTMS effects. One is related to brain- derived neurotrophic factor (BDNF) val/met polymorphism that regulates the propensity to synaptic plasticity. LTP and LTD are only induced in experimental animals with a val/val genotype, and rTMS seems to be effective only in humans with the same genotype (Cheeran et al. 2008). The other one is the dopamine D2 receptor C957T polymorphism that seems to determine thermal sensitivity and rTMS effects. Subjects with T/T genotype are more likely to show analgesic changes in the thermal threshold measurements after rTMS and, initially, they are more sensitive to thermal stimuli than are subjects with C/T or the C/C genotype (Jääskeläinen et al. 2014).

2.8.2 Therapeutic use of repetitive transcranial magnetic stimulation (rTMS)

During the last decade, rTMS has been successfully and safely used for the treatment of various clinical entities. In 2014, a group of European experts established evidence-based guidelines for the therapeutic use of rTMS (Lefaucheur et al. 2014). The level A (definite efficacy) evidence was defined for the analgesic effect of HF rTMS of the primary motor cortex (M1) contralateral to the neuropathic pain and the antidepressant effect of HF rTMS of the left dorsolateral prefrontal cortex (DLPFC). A more recent meta-analysis by the European Academy of Neurology (EAN) established the weak recommendation of rTMS for M1, and an inconclusive recommendation of rTMS for DLPFC for neuropathic pain (Cruccu et al. 2016). This recommendation was mainly due to the lack of high standard, randomized, placebo-controlled studies with representative patient samples. At the moment, the evidence of rTMS efficacy for neuropathic pain is approximately similar to spinal cord stimulation (a routine treatment for neuropathic pain) and motor cortex stimulation (MCS). Further, results have been better with neuronavigated rTMS for both neuropathic pain (Ayache et al. 2016) and major depression (Fitzgerald et al. 2009).

In the evidence-based guidelines (Lefaucheur et al. 2014), a level B recommendation (probable efficacy) was defined for the antidepressant effect of LF rTMS of the right DLPFC, HF rTMS of the left DLPFC for negative symptoms in schizophrenia, and LF rTMS of contralesional M1 for chronic motor stroke (a level C for post-acute motor stroke). A Level C (possible efficacy) recommendation was established for several disorders, such as the analgesic effect of HF rTMS of M1 contralateral to pain in complex regional pain syndrome type I, the anti-parkinsonian effect of HF rTMS of bilateral (multiple) sites in M1, the anti-epileptic effect of LF rTMS in focal epilepsy, and LF rTMS of the left temporoparietal cortex for auditory hallucinations and tinnitus (Lefaucheur et al. 2014).

Side effects of rTMS are rare and minor; mild headache due to local muscle contractions during the stimulation can occur in approximately 5% of the patients. The most serious possible side effect is an epileptic seizure, but this occurs extremely rarely, if current safety standards for stimulation are applied (Rossi et al. 2009). Absolute contraindications to rTMS are the same as for magnetic resonance imaging (MRI): The presence of magnetically active metallic intracorporeal appliances (e.g. cochlear implants and cardiac pace makers). Relative contraindications include epilepsy (although LF rTMS is, in fact, currently under study for the treatment of drug resistant status epilepticus) or an increased risk of seizures, severe or recent heart disease, and pregnancy (Lefaucheur et al. 2014).

2.8.3 Repetitive transcranial magnetic stimulation for chronic tinnitus

TMS pulses given at low frequencies (≤ 1 Hz) have been shown to decrease cortical excitability both in experimental settings and in humans. This finding forms the basis for using LF rTMS to treat chronic tinnitus patients, in whom hyperactivity of the auditory cortex has been observed in functional brain imaging studies (Plewnia et al. 2007). Over 100 papers on the topic have been published since 2003. A responder is usually defined as showing tinnitus reduction of more than 30-40% on a visual analogue scale or more than 5-10 points decrease in a tinnitus questionnaire score (Lefaucheur et al. 2014).

Several studies on rTMS for tinnitus have demonstrated moderate benefit (Eichhammer et al. 2003; Kleinjung et al. 2005; Plewnia et al. 2007; Rossi et al. 2007; Khedr et al. 2008; Anders et al. 2010; Marcondes et al. 2010; Mennemeier et al. 2011; Folmer et al. 2015). However, some of the recent controlled studies have not shown significant differences between active and placebo treatments (Hoekstra et al. 2013; Piccirillo et al. 2013; Langguth et al. 2014; Landgrebe et al. 2017). Notably, a recent multicenter, RCT on 163 tinnitus patients demonstrated 1-Hz-rTMS over the left temporal cortex being well tolerated, but not superior to the placebo rTMS (Landgrebe et al. 2017).

For the evidence-based guidelines for the therapeutic use of rTMS in tinnitus, 20 original placebo-controlled studies with at least 10 tinnitus patients were analyzed (Lefaucheur et al. 2014). They concluded a level C (possible efficacy) recommendation for repeated sessions of LF rTMS of the temporoparietal cortex (on the left hemisphere or contralaterally to the affected ear). A meta-analysis of 20 RCTs (720 patients) concluded there was a moderate efficacy of LF rTMS for chronic tinnitus: The odds ratio for therapeutic success, as defined by a THI decrease of 7 points or more, was at least 15 times greater in the active rTMS group (Soleimani et al. 2016). A recent review of rTMS was done for tinnitus evaluated studies published between 2014-2016, and it confirmed the possible efficacy of LF rTMS on the temporoparietal region. However, it concluded that rTMS benefit is modest and temporary, and the long-term clinical impact still remains to be demonstrated (Londero et al. 2017).

Most of the studies done have applied LF rTMS on the left temporoparietal cortex/AC or contralaterally to the tinnitus ear (Lefaucheur et al. 2014); however, in some studies rTMS has been applied bilaterally (Hoekstra et al. 2013) or even at multiple sites, including non-auditory brain areas, like DLPFC (Park et al. 2013; Lehner et al. 2013; Lehner et al. 2016). LF rTMS is the most studied, but there are some studies that are investigating HF rTMS for tinnitus (De Ridder et al. 2005; Khedr et al. 2008). Stimulation protocols, including the number of the treatment

sessions and pulses per session, stimulus intensity (the percentage of the resting motor threshold, RMT), as well as outcome measures and the duration of the follow-up, have varied throughout the studies. Further, in most studies, patient samples have been rather small and heterogeneous (Soleimani et al. 2016).

In the early studies, rTMS was positioned according to external anatomical landmarks or EEG 10/20 electrode locations (Langguth et al. 2006; Lefaucheur et al. 2014), but increasingly, in the more recent studies, some neuronavigational methods have been used. In a recent meta-analysis of rTMS for tinnitus, half of the analyzed studies used navigated rTMS (Soleimani et al. 2016). Currently, the available studies do not yet demonstrate clear evidence for the superiority of navigated TMS for tinnitus treatment (Langguth et al. 2010; Langguth et al. 2014; Noh et al. 2017b); thus, the role of neuronavigated rTMS in tinnitus treatment remains an open question.

A longer duration of tinnitus (De Ridder et al. 2005; Khedr et al. 2008), hearing loss (Kleinjung et al. 2007), and older age may reduce rTMS treatment efficacy (Langguth et al. 2008). However, in a study of 538 tinnitus patients treated with rTMS, no good demographic or clinical predictors for the treatment outcome were found (Lehner et al. 2012). In addition, patients with higher tinnitus symptom scores at the baseline did have more pronounced score reductions than patients with low baseline scores.

As the research findings are inconclusive, tinnitus guidelines do not yet recommend rTMS for the routine treatment of tinnitus (Tunkel et al. 2014). Additionally, tinnitus reduction after rTMS is usually partial and transitory, containing large inter-individual variations (Burger et al. 2011; Lefaucheur et al. 2014), and further, the long-term efficacy of rTMS is obscure. More research is also needed on rTMS maintenance therapy.

2.9 Other electromagnetic brain stimulation techniques

2.9.1 Non-invasive techniques

2.9.1.1 Transcranial direct current stimulation (tDCS)

Transcranial direct current stimulation (tDCS) is a form of non-invasive brain stimulation in which the cortical neuronal activity level is modified by the application of weak direct current on the brain cortex with electrodes (Lefaucheur et al. 2017). As described earlier, neuroimaging has demonstrated abnormalities of brain activity, connectivity and metabolism in the AC, as well as, in other brain

regions of tinnitus patients (De Ridder et al. 2014c). These changes in the auditory cortical area have led to the hypothesis that it may be possible to treat tinnitus by modulating these abnormalities via a stimulation of the brain with tDCS. This treatment is considered a safe treatment option, with only minor side effects, including local itching/tingling sensations, fatigue, or headache (Poreisz et al. 2007). The easy management and low cost of tDCS devices allow even home use. TDCS influences neuronal spontaneous firing, thereby causing a subthreshold shift of resting membrane potentials toward either depolarization or hyperpolarization, which depends on the current flow direction relative to the axonal orientation (Bindman et al. 1962).

Elucidated by TMS (an increase/decrease in the amplitude of MEP), anodal tDCS has been shown to increase the excitability of the underlying cortex, whereas cathodal tDCS decreases that outcome (Nitsche & Paulus 2000). A short stimulation duration (several seconds) induces excitability changes, which do not relevantly outlast the stimulation period, but a longer stimulation duration (20–30 minutes) induces excitability changes that last for several hours (Nitsche & Paulus 2001). In addition to local effects, tDCS has also connectivity effects via brain cortical and subcortical networks (Keeser et al. 2011).

In 2017, a group of European experts gathered the knowledge on the therapeutic use of tDCS for evidence-based guidelines (Lefaucheur et al. 2017). The analysis included only studies based on repeated tDCS sessions with the placebo tDCS for control. No Level A (definite efficacy) recommendation was proposed for any indication. A Level B recommendation (probable efficacy) was proposed for fibromyalgia, a major depressive episode without drug resistance, and addiction/craving, and Level C (possible efficacy) was recommended for chronic lower limb neuropathic pain secondary to spinal cord lesion. Conversely, the Level B recommendation (probable inefficacy) was issued in the absence of clinical effects for drug-resistant major depressive episode and tinnitus. For the tinnitus treatment guidelines, only 4 original RCTs, including at least 10 patients who received active tDCS of the left temporal cortex (with right orbitofrontal cathode) for multiple sessions, were included (Shekhawat et al. 2013; Teismann et al. 2014; Forogh et al. 2016; Hyvärinen et al. 2016). All studies showed no difference between active and placebo tDCS in their treatment efficacy for tinnitus.

2.9.1.2 Transcutaneous vagus nerve stimulation (tVNS)

Transcutaneous vagus nerve stimulation (tVNS) is a safe (at least for patients with no history of cardiac disease) and a non-invasive form of VNS suitable for prolonged use (Hoare et al. 2016). TVNS is based on the existence of an afferent sensory branch of the vagus nerve, which innervates the outer ear canal and parts

of the auricle (Ylikoski et al. 2017). This auricular branch of the vagus nerve projects centrally to the nucleus of the solitary tract in the brain stem. It has been demonstrated by fMRI and EEG recordings that the tVNS of the auricular branch activates the central vagal pathways in the same way as an implanted VNS (Kraus et al. 2007; Dietrich et al. 2008; Polak et al. 2009). The medial part of the tragus and concha region have been the main target area for tVNS.

Several studies investigating the safety and efficacy of tVNS, either alone or paired with acoustic stimulation for tinnitus, have been executed in recent years (Lehtimäki et al. 2013; Kreuzer et al. 2014; Hyvärinen et al. 2015; Ylikoski et al. 2017). These studies have mostly been experimental pilot studies showing either some or no therapeutic effect on tinnitus. Lehtimäki et al (2013) conducted a pilot study of tVNS using sound therapy (music filtered by any frequencies that resembled the patients's tinnitus) for 10 patients. The researchers concluded that the treatment produced improvement of mood and a decrease in tinnitus handicap scores, indicating reduced tinnitus severity. Additionally, the safety of the tVNS was confirmed, as no adverse events were reported.

2.9.1.3 Non-invasive electrical stimulation

Tinnitus suppression via electrical stimulation of the preauricular skin, mastoid, eardrum, promontory, or round window and within the cochlea has been examined from the 1960s with 7-82% of these patients reporting some relief in their tinnitus (Hoare et al. 2016). More recent studies have concentrated on the non-invasive electrical stimulation of the ear (Mielczarek et al. 2013; Mielczarek & Olszewski 2014; Lee et al. 2014; Mielczarek et al. 2016). The exact mechanisms of this treatment are unclear although it has been proposed that this therapy leads to hyperpolarization of neural fibrils, thus inhibiting a spontaneous firing rate by changing the basal membrane potential, presumably due to increased microcirculation of the auditory pathways (Lee et al. 2014). Further, a change in the cortical activity of the central temporal and frontal regions has been observed after electrical stimulation of the ear (Mielczarek et al. 2016). However, it remains unclear whether this change is primary or secondary to peripheral auditory excitation.

Mielczarek et al. (2013) examined 80 tinnitus patients and divided them into two groups. In Group I, direct current electrical stimulation of the external ear canal (the active electrode immersed inside the external ear canal and filled with saline, and the passive electrode placed on the forehead) was performed for 15 sessions. In Group II, the same electrical stimulation was given together with cervical spine kinesitherapy. For the tinnitus questionnaires, improvement was observed in Group I, in 43% of ears and in Group II, 33%, respectively. Interestingly, the

kinesitherapy did not have any potentiating influence. According to the authors, electrical stimulation with the application of current frequencies compatible with tinnitus frequencies (selective electrical stimulation) was an efficient method for severe tinnitus (Mielczarek et al. 2013). The same research team conducted a double-blind, RCT of direct current electrical stimulation (15 times) of the ear on 120 tinnitus patients (Mielczarek & Olszewski 2014). After the treatment, in the active group, in 40 ears (34%) the tinnitus disappeared, and in the placebo group, the tinnitus disappeared in 4 ears (6%). After 30 and 90 days, significant changes were still observed in the active group, but not in the placebo group. However, the tinnitus was not measured using a multi-item tinnitus questionnaire, so these results should be considered with caution. Additionally, there was an improvement in the audiometric thresholds in the active group, with patients also reporting subjective improvement in 30% of the ears. No harmful effect of using direct current on the hearing organ was observed.

Lee et al. (2014) conducted a RCT on the effectiveness of transcutaneous electrical nerve stimulation (TENS) applied to the external pinna in 65 tinnitus patients. These patients received TENS treatment twice a week for 4 weeks. THI and VAS scores were assessed before and after this electrical stimulation. In the active group, 62% revealed subjective improvement in tinnitus after the treatment. Symptomatic improvement in the active group was maintained for 1 month in most patients, but only two patients had any long-term improvement for up to three months. TENS seemed to be more effective in patients with low-frequency tinnitus or with a mild hearing loss. More randomized research with sufficient patient samples is still needed to determine the role of electrical stimulation of the ear on tinnitus treatment.

2.9.2 Invasive techniques

2.9.2.1 Motor cortex stimulation (MCS)

For motor cortex stimulation (MCS), stimulation electrode(s) are surgically implanted epiduraly on the sensorimotor cortex, with particular attention being paid to the primary motor area (M1) (Sukul & Slavin 2014). MCS has been used for movement disorders, including Parkinson's disease, dystonia, essential tremor, and poststroke spasticity with variable results (De Ridder et al. 2017). Mostly, MCS has been used for pain treatment, like an intractable spinal cord injury and neuropathic facial and post-stroke pain. Generally, patients are referred for MCS when they suffer from chronic and severe pain, and it has become refractory to other treatment options (Sukul & Slavin 2014). MCS has been shown to have a significant effect on chronic pain, including neuropathic pain conditions (Cruccu et al. 2007); a weak recommendation was given for pain management in a recent

meta-analysis due to the small number of RCTs (Cruccu et al. 2016). MCS has not been used for tinnitus treatment (De Ridder et al. 2017).

2.9.2.2 Auditory cortex stimulation (ACS)

The first report of invasive electrical stimulation in tinnitus was introduced by De Ridder et al. (2004), who demonstrated the suppression of tinnitus in one patient following focal epidural electrical stimulation of the primary AC (De Ridder et al. 2004). This patient had severe left-sided tinnitus following a total loss of hearing in the left ear (a cochlear nerve lesion), and the tinnitus was rated as a 9 on a 10-point VAS. Initially, TMS was applied to the right AC following fMRI to identify HG. The tinnitus was completely abolished beyond the duration of TMS stimulation. Subsequently, an extradural electrode was implanted onto the right AC for electrical stimulation via a neurostimulator. With auditory cortex stimulation (ACS), this patient's tinnitus disappeared completely, but three weeks after the operation, high-pitched tinnitus returned. It was suggested this reoccurrence was due to cortical plasticity in response to constant stimulation at the high-frequency areas. The exact mechanisms for how electrical stimulation of the cortex eliminated the tinnitus in the first instance remained obscure.

Since then, a few studies have been conducted to investigate the effects of intracranial ACS on tinnitus (De Ridder et al. 2006; Seidman et al. 2008; De Ridder et al. 2011b). Electrodes were implanted either onto the primary or the overlying secondary AC. De Ridder et al. (2011) reported a series of 43 patients who benefitted transiently from two separate placebo-controlled TMS sessions and were implanted with AC electrodes. The average tinnitus reduction was 53% for the total group, but in 33% of the patients the ACS was not efficient. In the future, ACS may become a valuable treatment option for severe refractory tinnitus. However, better understanding of the pathophysiology of tinnitus, new tools to predict efficacy, new stimulation designs, and possibly other stimulation targets may be needed to improve these results (De Ridder et al. 2017).

In addition to ACS, case reports of invasive stimulation of the DLPFC (De Ridder et al. 2012) and the dorsal ACC (De Ridder et al. 2016) for tinnitus have also been published with promising results.

2.9.2.3 Deep brain stimulation (DBS)

Deep brain stimulation (DBS) involves the surgical implantation of a neurostimulator within the brain to deliver electrical pulses (Hoare et al. 2016). The treatment has been used with variable success to treat several neurological disorders, mostly movement and affective disorders, such as Parkinson's disease

and essential tremor (Kumar et al. 1998), but also pain and epilepsy (Cruccu et al. 2016). Thus far, the DBS effects for chronic pain have been inconclusive.

DBS has been only experimentally investigated for tinnitus, and these studies have primarily focused on alleviating other co-existing conditions, like Parkinson's disease or tremor (Shi et al. 2009; Cheung & Larson 2010; Torres et al. 2010). In tinnitus, DBS theoretically aims to interfere with the communication between different parts of the brain involved in tinnitus by modifying or inhibiting the abnormal neural signal from reaching the AC (Hoare et al. 2016). Many studies have shown that the effects of DBS occur mainly in the subcortical (but also the cortical) structures, including the thalamus and the inferior cortex, which are assumed to be involved in tinnitus. Electrodes have been placed (in the thalamus or) subthalamic nucleus. Some patients have reported tinnitus relief, but no conclusions of the efficacy can be offered because of the experimental nature of the studies and their very limited sample sizes.

2.9.2.4 Chronic electrical vestibulocochlear nerve stimulation (VCNS)

Chronic electrical vestibulocochlear nerve stimulation (VCNS) is an invasive, alternative treatment option for intractable tinnitus (Hoare et al. 2016). It is based on the assumption that tinnitus is caused by a decreased afferent input to the vestibulocochlear nerve and other central auditory pathways (Bartels et al. 2007). In VCNS, the stimulation electrode is surgically implanted around the vestibulocochlear nerve (using a retrosigmoid approach), and connected to a pulse generator that is placed under the skin. In that way, the auditory pathways are stimulated directly. Only experimental studies with up to 10 patients have been conducted thus far on this topic (Bartels et al. 2007; van den Berge, Minke J C et al. 2017). The results have been encouraging with the majority of the patients experiencing a significant decrease in THI score, and their tinnitus transforming into a more bearable sound. However, complications included hearing deterioration and vertigo; therefore, this alternative treatment option needs further large scale study with a proper selection of patients and placebo control.

2.9.2.5 Vagus nerve stimulation (VNS)

As stated before, auditory stimulation alone seems not to be enough to influence plastic changes in the brain. Therefore, some studies have been investigating the forebrain cholinergic and noradrenergic systems that play a significant role in modulating cortical plasticity (Hoare et al. 2016). Experimental studies have shown that electrical stimulation of the cholinergic nucleus basalis can induce pronounced and long-lasting changes in cortical reorganization (Kilgard & Merzenich 1998a), which has led to the assumption that pairing auditory

stimulation with electrical stimulation could be used for tinnitus treatment (Kilgard & Merzenich 1998b). Nucleus basalis stimulation can be achieved using much less invasive vagus nerve stimulation (VNS) (Engineer et al. 2013).

VNS consists of a pacemaker-like, electric pulse generator that is surgically implanted in the chest wall. The electrode wires are threaded under the skin and woven around the left vagus nerve at neck level. The procedure is invasive and carries both short- and long-term risks, including infection or inflammation at the surgical site, hoarseness during stimulation, transient left vocal cord hypomobility, and a temporary increase in tinnitus symptoms (Hoare et al. 2016). Thus far, VNS has shown some treatment effect for epilepsy (Ben-Menachem 2001) and depression (Cristancho et al. 2011); in fact, it is now approved for drug-resistant epilepsy and depression treatment by the U.S. Food and Drug Administration (Hoare et al. 2016).

Several studies have investigated the safety and efficacy of the VNS when paired with acoustic stimulation (tones excluding the tinnitus-matched frequency) with promising results (De Ridder et al. 2014a; De Ridder et al. 2015; Tyler et al. 2017). Tyler et al (2017) evaluated VNS paired with sound or a control in 30 chronic tinnitus patients, and 50% of the patients in the paired VNS group showed clinically meaningful improvements compared to 28% in the controls. At the one year control, 50% of the patients had a clinically meaningful response with the paired VNS. The authors concluded that this new treatment modality may be safe and effective for a sub-group of tinnitus patients, but it still needs further study.

3 AIMS OF THE STUDY

The aims of the present study were:

3.1 To investigate the feasibility and effects of electric field (E-field) navigated rTMS for chronic, intractable tinnitus and analyze the influence of several factors related to the protocol for the treatment results. To provide information, such as sample size calculations, for the upcoming randomized controlled trial of rTMS for tinnitus. (Study 1, Original Article I)

3.2 To investigate the effects of E-field navigated rTMS (targeted to the representation area that roughly corresponds to the perceived tinnitus pitch) compared to a placebo rTMS for chronic tinnitus. To evaluate the long-term effects of E-field rTMS for tinnitus. (Study 2, Original Article II)

3.3 To investigate whether targeting the region overlying the AC with neuronavigated rTMS (nrTMS) based on an individual structural head MRI is superior to non-navigated rTMS that utilizes the 10-20 EEG electrode location system for treatment of chronic tinnitus. To evaluate the long-term effects of rTMS for tinnitus. (Study 3, Original Article III)

3.4 To investigate the current and lifetime prevalence of psychiatric Axis I (main psychiatric diagnoses) and Axis II disorders (personality disorders) using the structured diagnostic interview (SCID I and II) in patients with chronic tinnitus. To examine the temporal relationship of psychiatric disorders and the occurrence of tinnitus. To evaluate current psychiatric symptoms, including dissociative experiences, using self-report questionnaires. (Study 4, Original Article IV)

Outline of the Work

This work consists of the four Studies (1-4), on which the four Original Articles (I-IV) are based.

All four Studies have a connection to each other. Study 1 was executed to serve as a pilot for a prospective RCT on navigated rTMS for chronic tinnitus (Study 2). Studies 2 and 3 had parallel (the same inclusion and exclusion criterion), but separate patient groups. For Study 4, the patient groups of Studies 2 and 3 were joined.

4 PATIENTS AND METHODS

4.1 Patients

Table 2. Demographic and tinnitus data on the patients in Studies 1-4.

Study	Original Article	Number of Patients (initially recruited)	Age (years) mean (SD)	Women / Men	Duration of tinnitus in years mean (SD)	THI Score mean (SD)	Tinnitus intensity in VAS mean (SD)	Tinnitus annoyance in VAS mean (SD)	Tinnitus distress in VAS mean (SD)
1	I	13 (14)	53 (13.2)	3 / 10	Range 1-20*	Not measured	7.1 (1.8)°	7.0 (1.8)[1]	Not measured
2	II	39 (42)	50.3 (11.8)	12 / 27	5.1 (2.5)	30 (quartiles 14-44)[2]	59.2 (14.4)	51.5 (21.2)	49.7 (20.0)
3	III	40 (44)	52.9 (11.7)	20 / 20	5.8 (3.2)	42.2 (18.8)	62.2 (12.8)	56.1 (16.6)	54.6 (15.9)
4	IV	83 (86)[3]	51.7 (11.5)	34 / 49	5.5 (2.9)	32 (quartiles 18–56)[2]	60.5 (13.7)	53.7 (18.8)	52.1 (17.9)

* The mean duration of tinnitus was not calculated, as two patients reported their duration being "several" years, but without any exact numbers.
° The mean tinnitus intensity in NRS
[1] The mean tinnitus annoyance in NRS
[2] The median THI scores (and quartiles), as THI scores were not normally distributed
[3] The same patients as in Studies 2-3
Abbreviations: SD, Standard Deviation; THI, Tinnitus Handicap Inventory; VAS, Visual Analog Scale (0-100); NRS, Numeric Rating Scale (0-10)

A total of 96 patients with chronic, continuous, and disturbing tinnitus were evaluated in Studies 1-4. None of the patients had any contraindications for rTMS treatment (Rossi et al. 2009), such as magnetically active, metallic intra-corporeal appliances (e.g. cochlear implants and cardiac pace makers), epilepsy or increased risk of seizure (e.g. brain tumour, stroke, active alcohol abuse), active bipolar disorder, severe heart disease, migraine, or pregnancy. None of the patients had previously been treated with rTMS.

4.1.1 Study 1 (Original Article I)

This study took place at the Department of Ear, Nose and Throat Diseases (ENT) and the Department of Clinical Neurophysiology at Turku University Hospital (TUCH) during 2011-2014. Inclusion criteria were severe (intensity of at least 5/10 on the Numeric Rating Scale, NRS), chronic (duration at least one year), otherwise intractable, and a disabling tinnitus that severely interfered with the participants' everyday life activities. Previous tinnitus treatments consisted of repeated counselling with an ENT-specialist and a psychologist or psychiatrist, medication trials with anti-depressants or betahistine, but with no success. Consecutive clinical patients that fulfilled these criteria and were willing to participate in the study were recruited from the ENT department of the TUCH between autumn 2011 and spring

2013. One patient had to be rejected from the study due to having previous brain tumor surgery.

Altogether, 13 patients (3 women, 10 men) between 30-73 years (mean age 53 years, SD 13.2) with mean tinnitus intensity in NRS (0-10) 7.1 (SD 1.8), and annoyance 7.0 (SD 1.8) participated in the study. Of these patients, 8/13 had bilateral tinnitus, and the other 5 patients had more lateralized tinnitus. Only 2 patients had normal hearing, and the other patients suffered from variable sensorineural hearing deficit, mostly in the high frequency range. Of these patients, 8/13 suffered from depression, and 8/13 used prescription medication that affected the central nervous system. All patients underwent a 3D-MRI of the head to rule out possible treatable causes for tinnitus and provide anatomical guidance for neuronavigated TMS. None of the patients had any tumours showing in their head MRI, but some did have minor structural changes, such as mild leucoaraiosis. Table 1 in the Original Article I shows the demographic data, tinnitus and hearing characteristics, medications, and head MRI findings in detail.

4.1.2 Studies 2-4 (Original Articles II-IV)

Studies 2-4 constituted a larger RCT project (Tinnitus rTMS 2013) that evaluated rTMS in the treatment of chronic tinnitus. The project was registered on ClinicalTrials.gov (ID NCT 01929837). Studies 2-4 shared the same inclusion criteria: chronic (6 months–10 years), uni- or bilateral tinnitus with an intensity of at least 4/10 on the NRS scale in the age group of 18–65 years. Pulsatile tinnitus and objective tinnitus were exclusion criteria. The patients had been treated in TUCH (Studies 2 and 4) or in Satakunta Central Hospital (SatKS) (Studies 3 and 4) because of their tinnitus. First, an information letter about the study was sent to eligible patients, who were then contacted by phone and asked whether they still had refractory tinnitus with an average intensity of at least 4/10 on the NRS. All the patients underwent a complete audiological (by a nurse who specialized in audiology) and otological investigations (by an ENT-specialist, HS) and also a head 3D-MRI to rule out possible treatable causes for their tinnitus and provide anatomical guidance for the neuronavigated TMS.

4.1.2.1 Study 2 (Original Article II)

This study took place at the Departments of ENT and Clinical Neurophysiology at TUCH during 2013–2015. All the tinnitus patients (425 patients) born between 1948 and 1995 treated at the Department of ENT in TUCH between January 2009 and March 2013 were reviewed using electronic patient archives. Figure 1 in the Original Article II shows the flow chart. For the study, 42 patients with the highest NRS numbers were chosen and randomized using a random permuted block

design; 22 patients for the active rTMS group and 20 patients for the placebo rTMS group. In the active rTMS group, one patient did not receive treatment according to the protocol and 2 patients discontinued intervention (both felt the stimulation uncomfortable and had difficulty arranging time for the study). Altogether 39 patients (27 males and 12 females) ages between 23–65 years (mean age 50.3 years, SD 11.8) with mean tinnitus duration of 5.1 (SD 2.5) years completed the study and were included in the final data analysis. The baseline mean tinnitus intensity in VAS (0-100) was 59.2 (SD 14.4), annoyance 51.5 (SD 21.2), distress 49.7 (SD 20.0) and median THI scores 30 (quartiles 14-44).

There were no tumours in the head MRIs, but 4 patients did have mild leucoaraiosis, 6 had mild atrophy and 3 had small benign cyst(s) in the brain. All patients were right-handed, except for one in the placebo group. Table 1 in the Original Article II lists the characteristics of the 19 patients in the active group and the 20 patients in the placebo group in detail. Comparing the baseline characteristics of both groups, their only statistically significant difference ($p=0.03$) was in the mean tinnitus loudness match in the left ear, which was 24.5 (SD 26.1) in the active group and 43.9 (SD 26.9) in the placebo group, respectively. In the active group, 8 patients suffered from lifetime depression (either previous or current) diagnosed using SCID and 6 patients did in the placebo group, respectively ($p=0.43$). The baseline BDI scores were low with a median of 5.0 (quartiles 2.0–9.0) in the active and 4.0 (quartiles 0–10.5) in the placebo group ($p=0.69$).

4.1.2.2 Study 3 (Original Article III)

The study took place at the Departments of ENT and Clinical Neurophysiology at SatKS during 2013–2016. All tinnitus patients (197 patients) who were treated at the Department of ENT in SatKS between January 2012-March 2013 were found in the patient archives. Figure 1 in the Original Article III shows the patient recruitment process. In this regard, 44 patients with the highest NRS numbers were chosen; 3 patients withdrew (difficulties in arranging time for the treatment and controls) and one was excluded (suffered a trancient ischemic brain attack) before the start of the treatment. Further, 40 patients were randomized using a random permuted block design; 20 patients to the nrTMS group and 20 patients to non-navigated rTMS group. All 40 patients (20 males and 20 females), ages between 19-65 years (mean age of 52.9 years, SD 11.7) with a mean tinnitus duration of 5.8 (SD 3.2) years completed the study and were included in the analyses. The baseline mean tinnitus intensity in VAS (0-100) was 62.2 (SD 12.8), annoyance was 56.1 (SD 16.6), distress was 54.6 (SD 15.9) and THI scores were 42.2 (SD 18.8).

There were no tumour findings in the head MRIs, but one patient had a minor benign cyst; another had minor unspecified signal changes in the brain. All patients

were right-handed, except for one in the non-navigated group. Table 1 in the Original Article III lists the characteristics of the patients in both groups in detail. The groups did not differ in any of their baseline characteristics (p=0.087-1.0). In both groups, only one patient suffered from current depression, diagnosed using SCID, and BDI scores were low at 6.0 (quartiles 4.0-9.0) in the navigated and 5.5 (quartiles 3.0-8.0) in the non-navigated group (p=0.39).

4.1.2.3 Study 4 (Original Article IV)

In Study 4, the patients from Studies 2 and 3 were evaluated together, including those patients who had discontinued the rTMS study, but had already been interviewed at the baseline using SCID. This study took place at the Departments of ENT and Psychiatry of TUCH and SatKS during 2013–2016. Taken all together, 83 patients (49 men or 59% and 34 women or 41%) with ages between 19-65 (mean 51.7, SD 11.5, median 56.0) and a mean tinnitus duration of 5.5 (SD 2.9, median 5.0) years were included in the analyses. The mean tinnitus intensity in VAS (0-100) was 60.5 (SD 13.7), annoyance 53.7 (SD 18.8), and distress 52.1 (SD 17.9). The median THI score was 32 (quartiles 18–56, range 2–94). The median PTA of 500, 1000, 2000 and 4000 Hz was 14.0 dB (quartiles 6.0–27.5, range 0–78) in the right ear and 14.0 dB (quartiles 6.0–28.8, range 0–83) in the left ear; therefore, the median PTA in both ears was within the normal range (0–20 dB). Table 3 in the Original Article IV lists the characteristics of these patients in detail. During the course of the study, one patient was discovered to have a concomitant bipolar disorder, but it was stable, and that individual was willing to continue in the study group.

4.2 Study designs

4.2.1 Study 1

This study on chronic tinnitus patients was conducted using an open, prospective, methodological pilot study design. All patients received 3–15 sessions of E-field navigated, active rTMS treatment to the left (or right) STG, with 3 patients also receiving stimulation to the left DLPFC for depression and 1 the right primary motor cortex (M1) for pain.

NRS values (from 0 to 10) were used to evaluate the severity of the tinnitus. Zero (0) represented the situation with no tinnitus or no annoyance, and ten (10) was the worst possible tinnitus intensity or annoyance the patients could imagine. If a patient declared two numbers, for example 5–6, the value was registered as 5.5. The Global Impression of Change scale (GIC scale from -3 to +3, in which -3

meant very much worse and +3 very much better than before the treatment and 0 meant no change) was used to evaluate the subjective benefit of the serial treatment.

The NRS value was first obtained at the baseline. The patients were asked to give a value for the average tinnitus intensity and annoyance level for the previous week. Then, the patients evaluated the NRS tinnitus intensity and annoyance immediately before and after each rTMS session, in the evening, and the following morning after the session using a tinnitus diary. As there were values missing in the diaries, the mean NRS values at the baseline and daily assessments after the first four (three in one patient) treatment sessions (immediately or in the evening of the treatment day), as well as at the end of the serial treatment right after the last rTMS session were chosen for the statistical analyses. A reduction of 30% or more in NRS value was considered to be a clinically significant change, as it is a commonly used cut-off point in most controlled trials on pain treatment (Dworkin et al. 2008). In addition, the GIC scale was used after the serial rTMS treatment to evaluate the subjective benefit of the treatment.

Additionally, other effects, such as the lateralization of tinnitus, changes in tinnitus frequency or quality, and possible side-effects, were registered. One patient felt difficulties in the self-rating of the tinnitus intensity and annoyance in the evening and the following morning. One patient was not able to evaluate the tinnitus immediately after the treatment session because the tinnitus was not discernible due to the sound generated by the TMS device. As tinnitus intensity may fluctuate during the day, this aspect may have caused some additional variability in the results. After the study, the data on long-term effects were collected retrospectively via the electronic patient archives as available.

4.2.2 Study 2

This study on chronic tinnitus patients was conducted using a prospective, randomized, single-blind, placebo-controlled design with parallel groups. The patients received 10 sessions of either E-field navigated, active rTMS or a placebo rTMS with the same device to the left STG/AC. At the baseline and after the serial treatment an audiogram (both air and bone thresholds) was obtained and a PTA of 500–4000 Hz calculated for both ears. Patients verbally described the pitch of tinnitus during each rTMS session. Additionally, the loudness (dB) and the pitch (Hz) of tinnitus were psycho-acoustically measured using a clinical audiometer at the baseline, after the serial treatment, and then 1 and 3 months after the rTMS. At these same time points, the patients assessed their tinnitus via the THI and VAS (between 0 (no tinnitus) and 100 (the worst tinnitus the patient could imagine) for tinnitus intensity, annoyance, and distress in everyday life. Additionally, the

patients rated their GIC, and the BDI and the Jenkins Sleep Evaluation Questionnaire (JSEQ) were used to monitor mood and sleep. At 6 months, the final control was a telephone interview that included NRS (0–10) concerning tinnitus intensity, the THI, and GIC. Structured psychiatric interviews (SCID Axis I and II) were conducted at the baseline.

4.2.3 Study 3

This study with chronic tinnitus patients was conducted in a prospective, randomized, single-blind design with parallel groups. The patients received 10 sessions of either neuronavigated rTMS or non-navigated rTMS (based on the 10-20 EEG localization system) with the same device on the left temporal area overlying AC. The same protocol and follow-up measurements were applied as used in Study 2.

4.2.4 Study 4

This study included all the chronic tinnitus patients of Studies 2-3 by reporting the results of the baseline psychiatric diagnostic interviews (SCID Axis I and II) and comparing them with the general population of the US National Comorbidity Survey Replication (NCS-R) (Kessler et al. 2005a; Lenzenweger et al. 2007). The SCID interviews diagnosing both current (previous month) and lifetime disorders were conducted either by a psychiatrist or a psychologist trained to use the instruments. The duration of the interviews ranged from 2 to 4 hours. A further division of the lifetime Axis I and II disorders was done for onset before and after the onset of tinnitus. Subjective psychiatric symptoms were evaluated using the baseline self-report questionnaires, including the BDI, the Symptom Checklist-90 (SCL-90), and the Dissociative Experiences Scale (DES). Tinnitus and hearing were assessed using the baseline THI and VAS. The baseline audiogram (both air and bone thresholds) was measured for decibels hearing level (dB HL) and a PTA of 500–4000 Hz calculated for both ears. In addition, the patients' personal and somatic histories were taken during the interview. Patients' medical records at TUCH and SatKS were also available for the researchers.

4.3 Clinical evaluation

4.3.1 Tinnitus Handicap Inventory (THI)

The Tinnitus Handicap Inventory (THI) (Newman et al. 1996) is a self-report measure that can be used to quantify the impact of tinnitus on daily life. The THI consists of 25 questions with cut-off scores for severity of tinnitus: 0–16 for slight

(Grade 1), 18–36 for mild (Grade 2), 38–56 for moderate (Grade 3), 58–76 for severe (Grade 4) and 78–100 for catastrophic (Grade 5) tinnitus. Suggested grading is described as follows. “Grade 1: Only heard in a quiet environment, very easily masked. No interference with sleep or daily activities; Grade 2: Easily masked by environmental sounds and easily forgotten with activities. May occasionally interfere with sleep but not daily activities; Grade 3: May be noticed, even in the presence of background or environmental noise, although daily activities may still be performed. Less noticeable when concentrating. Not infrequently interferes with sleep and quiet activities; Grade 4: Almost always heard, rarely, if ever, masked. Leads to a disturbed sleep pattern and can interfere with the ability to carry out normal daily activities. Quiet activities affected adversely; Grade 5: All tinnitus symptoms at level of severe or worse” (McCombe et al. 2001).

There is no validated THI questionnaire in Finnish. The original English version of the THI was translated into Finnish to be used in this study. This Finnish version was back-translated into English to exclude any significant errors in translation. The cultural differences between the USA and Finland were supposed to be minor, and no further changes were done. The THI score was calculated according to the original scale (yes = 4, sometimes = 2, no = 0).

4.3.2 Visual Analog Scale (VAS) and Numeric Rating Scale (NRS)

The Visual Analog Scale (VAS) is a continuous scale, measuring subjective symptoms, like pain and tinnitus, that cannot be directly measured. Patients specified their level of symptom severity by marking a position along a 100-millimeter line between two end-points, 0 and 100. The VAS score between 0 (no tinnitus) and 100 (the worst tinnitus the patient could imagine) was asked of the patients for tinnitus intensity, annoyance, and average distress caused by tinnitus in everyday life. VAS intensity/loudness and annoyance have been tested to be valid and effective for measuring changes in tinnitus severity in chronic tinnitus (Adamchic et al. 2012).

The Numeric Rating Scale (NRS) offers a stepwise non-linear series from 0 to 10. The patient chooses the best number that matches the subjective severity of symptoms. The NRS has been widely used to assess self-reported pain intensity (Dworkin et al. 2008), but also for the evaluation of subjective tinnitus (Meikle et al. 2008). The range for NRS is from 0 to 10 (on an 11-point scale) with 0 representing a situation with no tinnitus or no annoyance and 10 representing the worst possible tinnitus intensity or annoyance a patient can imagine.

4.3.3 Global Impression of Change (GIC)

The Global Impression of Change (GIC) is a self-report measure that reflects a patient's belief about changes caused by a treatment. The GIC is a 7-point scale between -3 (very much worse) and +3 (very much improved), 0 meaning no change, and measured after treatment of pain or tinnitus (Meikle et al. 2008).

4.3.4 Beck Depression Inventory (BDI)

The Beck Depression Inventory (BDI) is a self-report questionnaire used for assessing depressive symptoms, and it is not a diagnostic instrument (Steer et al. 1999). The BDI includes 21 questions for measuring the severity of depressive symptoms with cut-off scores suggestive of minimal (0-13), mild (14-19), moderate (20-28), and severe (29-63) depression. The validated Finnish version of this inventory was used.

4.3.5 Jenkins Sleep Evaluation Questionnaire (JSEQ)

The Jenkins Sleep Evaluation Questionnaire (JSEQ) is a self-report instrument for the evaluation of sleep disturbances (Jenkins et al. 1988). The JSEQ consists of 4 items, including difficulties in initiating and maintaining sleep, experiencing nonrestorative sleep, and an item on the level of tiredness after a regular night sleep. The total score may be 0–20 with higher scores indicate greater sleep impairment. The validated Finnish version of this questionnaire was used.

4.3.6 Symptom Checklist-90 (SCL-90)

The Symptom Checklist-90 (SCL-90) is a self-report questionnaire used for assessing psychiatric symptoms (Derogatis 1977). The SCL-90 consists of 90 questions with a 5-point scale from 1 (not at all) to 5 (extremely) and evaluates psychological problems and symptoms of psychopathology for primary symptom dimensions of somatisation, obsessive-compulsiveness, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism, and additional items. The validated Finnish version of this inventory was used (Holi et al. 1998).

4.3.7 Dissociative Experiences Scale (DES)

The Dissociative Experiences Scale (DES) is a self-report instrument having 28 questions that screen for the different types of dissociative symptoms, including both problematic dissociative disorders and normal dissociative experiences, such as daydreaming (Bernstein & Putnam 1986). The DES is not a diagnostic instrument; therefore a high score only implies that a clinical assessment for

dissociation may be needed. The validated Finnish version of this instrument was used.

4.3.8 Structured Psychiatric Interviews (SCID Axis I and Axis II)

Diagnostics of Axis I psychiatric disorders, both current (previous month) and lifetime, as conducted using the structured clinical interview for the DSM-IV disorders (SCID-I) (First et al. 1997a). Axis I disorders, in the DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition) (American Psychiatric Association 1994) cover all psychiatric diagnostic categories, such as psychosis, depression, anxiety, panic disorder or social phobia, excluding mental retardation and personality disorders. The SCID-I consists of modules on mood episodes, psychotic symptoms, psychotic disorders, mood disorders, substance use disorders, anxiety disorders, somatoform disorders, eating disorders, adjustment disorder, and an optional module (acute stress disorder etc.).

Axis II disorders in the DSM-IV (American Psychiatric Association 1994) include personality disorders that are divided into three clusters: A represents odd and eccentric; B represents dramatic, erratic or emotional; and C, fearful and neurotic. Personality disorders, both current (previous month) and lifetime, were evaluated independently of the Axis I disorders using the SCID-II interview (First et al. 1997b).

The SCID was conducted by experienced clinicians trained to use the instrument. Ratings of the SCID are based on criterion items, and not answers to the questions. In other words, the interviewer makes a clinical judgement on whether a certain diagnostic criterion is met or is not. In previous studies, the SCID results have shown moderate to excellent inter-rater agreement and high levels of reliability maintained over time (Lobbestael et al. 2011; Zanarini & Frankenburg 2001). The validated Finnish version of the SCID-I and -II was used.

4.3.9 Audiometric Measurements

The audiometric measurements were conducted by experienced nurses who specialize in audiology. The measurements were taken in soundproof facilities using a Madsen Aurical audiometer EN 60645-1-2 (Madsen Electronics, Copenhagen, Denmark) and TDH-39 supra-aural earphones in accordance with the standard ISO 8253-1 (International Organisation for Standardization 1998). Masking was used when needed. The audiometer was calibrated according to ISO 389-1 (International Organisation for Standardization 2000). The audiometric thresholds for air-conducted, pure-tone stimuli were measured at the frequencies 125, 250, 500, 1000, 2000, 3000, 4000, 6000 and 8000 Hz for both ears. Bone-

conduction thresholds were established for the frequencies 250, 500, 1000, 2000 and 4000 Hz, if the air-conducted hearing threshold was higher than 15 dB at any frequency. A pure tone average (PTA) of 500–4000 Hz was also calculated for air-conducted thresholds for both ears.

The loudness (dB) and the pitch (Hz) of tinnitus were psycho-acoustically assessed for both ears by using a loudness/pitch match with the same clinical audiometer as the hearing was tested (Langguth et al. 2007a; Meikle et al. 2008).

4.4 Repetitive transcranial magnetic stimulation (rTMS)

In TUCH (Studies 1 and 2), an electric field (E-field) navigated TMS device, the NBS-TMS System 4.0 (Nexstim Ltd, Helsinki, Finland) was used. This navigation system requires a head 3D-MRI to be utilized in targeting the stimulation and visualizing the induced E-field and its computed estimated strength in Volts per meter (V/m) in real time during the treatment. An infrared tracking system recognizes the head tracker, the digitizing pen, and the biphasic figure-8 treatment coil. Outer landmarks are first marked with a pointer pen, and the system then translates these to head fraction coordinates. After that process, the registration system continually links the MRI image to the location of the patient's head and the stimulation coil during the session. The E-field and its "hotspot" (the exact stimulation spot) are shown on the MRI image on a computer screen to control the cortical target during the treatment.

This ''hot spot'' of stimulation has been shown to have an anatomical accuracy of a few millimetres, thus corresponding to the accuracy of direct intraoperative cortical electrical stimulation (Picht et al. 2011). The user can easily control the cortical target and the direction of the electric current vector during stimulation. During the treatment, the coil is fixed in the correct position by a coil holder, and the patient's head was resting on the chair. The stability of the coil was monitored throughout the treatment sessions in real time from the computer screen by a medical doctor or a trained technician. If the centre of the induced E-field moved away from the set target more than 3 mm, the stimulation was paused, and the coil was readjusted.

In SatKS (Study 3), the TMS device used was the Visor2 navigation system (ANT Neuro, Berlin, Germany), which is capable of showing in real-time the position of the coil and the calculated electric field in relation to the 3D-MRI of the patient's head. The Visor2 uses an infrared camera system with total accuracy better than 2 mm to link the MRI image to the location of the patient's head and the stimulation coil. The MagStim Rapid^2 -stimulator (Magstim Co., Whitland, Wales, UK) with

an air-cooled figure-8 coil with a biphasic pulse was used. In the Visor2, all parameters of the TMS stimulation session are registered, so it can be easily reproduced. The position of the coil was monitored throughout the treatment session by a trained technician and allowing for a 5 degree and 5 mm shift. If these limits were exceeded, the stimulation was paused, and the coil positioning was corrected.

Both in TUCH and in SatKS (Studies 1-3), before the serial rTMS treatment, the motor cortex was first activated by single, suprathreshold TMS pulses so as to locate the "hot spot" for thenar muscle activation. In TUCH, the motor evoked potential (MEP) responses were collected with an integrated electromyography (EMG)-unit in the Nexstim NBS 4.0 system using a 3 kHz sampling frequency. The signal was filtered with a band pass filter of 10-500 Hz. In SatKS, the Visor2 system integrates navigated TMS and EMG recording with a real-time E-field visualization of the stimulated brain areas. The EMG was recorded with Refa8-64 amplifier (TMS International, Enschede, The Netherlands) using a sampling rate of 2048 Hz. The EMG signal was filtered at the Visor2 system with a high pass filter of 10 Hz. The resting threshold for MEP of the contralateral thenar muscles (m. opponens pollicis) was then determined at that "hot spot" target. Self-adhesive surface electrodes were used to record the MEP; the primary motor area was located by moving the stimulating coil until the spot producing highest MEP was produced. Once the optimal position was located, the resting motor threshold (RMT) was determined by delivering single TMS pulses over the optimal position with up-and-down varying intensities to reach the RMT defined as the lowest TMS intensity (% of maximum output) capable of eliciting a small (> 50 μV) MEP in at least 50% trials while the investigated muscle was at rest. The RMT was determined as recommended by the International Federation of Clinical Neurophysiology (Groppa et al. 2012). Patients used ear plugs during the rTMS treatment sessions.

In Study 1, the patients received 3-15 sessions of 1 Hz E-field- navigated active rTMS treatment to the left (or right) STG/AC, with 3 patients also receiving 10 Hz rTMS stimulation to the left DLPFC and one to the right primary motor cortex (M1). Each rTMS session consisted of 1800-3000 pulses given at 90-110% of the RMT. Table 3 describes these rTMS stimulation protocols in detail.

In Study 2, patients received 10 session of either active or placebo rTMS over 2 weeks (five daily weekday sessions). Each session consisted of 4000 pulses at a continuous 1 Hz rate given to the left STG/AC at 100% of the RMT. In the active group, all patients received 10 full sessions, except for one patient for whom one session was only 2800 pulses (due to her delayed arrival). In the placebo group, 17 patients received 10 full sessions, 2 patients received 8, and 1 patient received only

6 full sessions (due to patient-related causes and technical problems with the NBS system). In the active group, the stimulation intensity was lowered from 100% to 95–80% for 5 patients because of annoying facial contractions. The left side was chosen based on the previous literature (Lefaucheur et al. 2014; Soleimani et al. 2016), which had mostly indicated that stimulation of the left auditory area is efficient, regardless of the tinnitus location (Burger et al. 2011; Lehner et al. 2012); yet some contradictory evidence exists as well (Kim et al. 2014). For placebo stimulation, a 15-cm plastic block was attached to the coil, preventing any effective E-field (attenuation to 0 – 4 V/m) from being induced within the cortical structures. However, the coil with the placebo block was never visible to the patients.

Table 3. The rTMS stimulation protocols used in Study 1. Modified from (Sahlsten et al. 2015).

Patient	RMT (%)	Number of rTMS sessions	Pulses/ session	Total amount of pulses / patient	Location of stimulation*	Intensity of stimulation (%)	E-field (V/m) at cortical target
1	35	10	1800, 3000[1]	22800	STG sin ↑[2]	110	66-84
2	49	4	1800	7200	STG sin ↑	110	97-124
3	30	4	1800	7200	STG sin ↓↑[3]	110	58-91
4	25	3	1800	5400	STG sin ↑	110	45-57
5	52	4	1800	7200	STG sin ↑	110	70-110
6	41	13	1800	23400	STG sin ↑[4]	90-100	62-83
7	57	8	3000	24000	STG sin ↑	90-100	78-110
8	35	15	2000	30000	STG sin ↑	90-110	50-75
9	46	10	2000	20000	STG sin ↑	90-100	59-91
10	36	10	2000	20000	STG sin ↑[5]	100	58-82
11	44	12	2000	24000	STG sin ↑[6]	100	80-116
12	36	5	3000	15000	STG sin ↑	100	74-84
13	50	9	2000,2500,3000[7]	25500	STG sin ↑[8]	100	80-103

* The arrow indicates the direction of the active E-field on the superior temporal gyrus (STG), as ↑ cranially, ↓ caudally.
[1] During the last four sessions, the number of pulses was 3000.
[2] One treatment was given on the right STG. During two sessions, a combined treatment attempt on the left dorsolateral prefrontal cortex (DLPFC) for depression (10 Hz, 100% RMT, 1000 pulses) was applied.
[3] During the first session, the active E-field was directed downward, causing slight hypomanic symptoms during the treatment day.
[4] During the last eight sessions, the stimulation of the right DLPFC for depression (10 Hz, 90% RMT, 1800 pulses) was combined for the treatment.
[5] During sessions 7, 8, 9 and 10, the treatment was applied both on the right side and the left side.
[6] During every session, the stimulation of the left DLPFC for depression (10 Hz, 90% RMT, 3000 pulses) was combined for the tinnitus treatment.
[7] During the first session, 2000 pulses were given; otherwise, 3000 pulses, except once, 2500 pulses.
[8] During every session, the stimulation of the right primary motor cortex (M1) hand representation area (10 Hz, 90% RMT, 1500-2000 pulses) was combined for the treatment of neuropatic pain.
RMT = resting motor threshold, STG = superior temporal gyrus, E-field = induced electric field during the sessions in volts per meter (V/m)

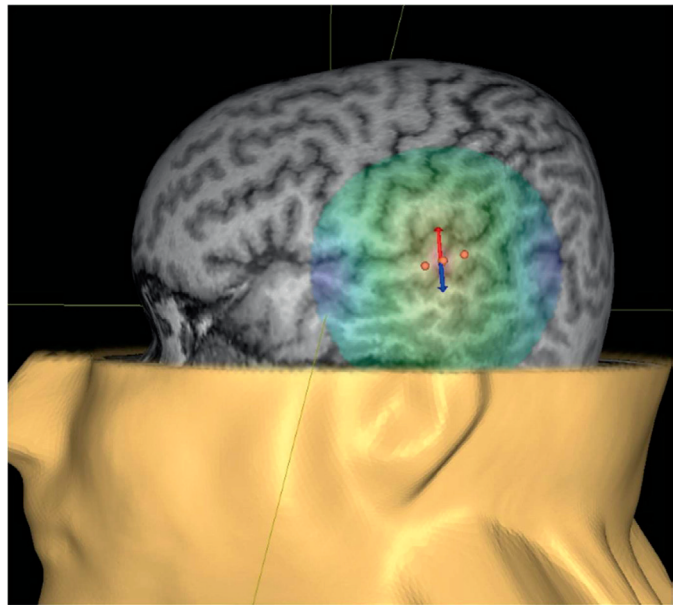


Figure 6. The stimulation-induced E-field and the current vector at the ‘‘hot spot’’ used in Studies 1 and 2. Reproduced with the permission of the copyright holders (Sahlsten et al. 2017).

Figure 6 shows the stimulation-induced E-field and the current vector at the ‘‘hot spot’’ used in Studies 1 and 2. The upward arrow (red) demonstrates the induced electric field vector on the cortical site at the left STG. The exact stimulation spot, the ‘‘hot spot”, is at the joining of the upward (red) and the downward (blue) arrows. The brightness of the arrows reflects the optimal tangential position of the coil. In Studies 1 and 2, the active E-field (the induced current flow direction of the first quarter cycle of the biphasic pulse) was directed upward. The stimulation targets (orange points in Figure 6) were marked at the left STG on the patients’ MRIs based on the individual gyral anatomy at the depth of 20-30 millimetres from the skull surface. The calculated electric field on the cortex (at the orange point) is also presented numerically as V/m on the screen (but not shown in the Figure). Since different pitches are tonotopically represented within the AC, namely, high frequencies in the posterior and lower frequencies in the anterior areas (Moerel et al. 2014) (but simplified in Figure 1b), we presumed that targeting rTMS to the representation area roughly corresponding to the perceived tinnitus pitch would better reduce the cortical hyperexcitability. The more posterior regions of the AC were targeted when tinnitus was high pitched (the most posterior point in Figure 6); if the pitch lowered during the treatment (based on the patient’s subjective

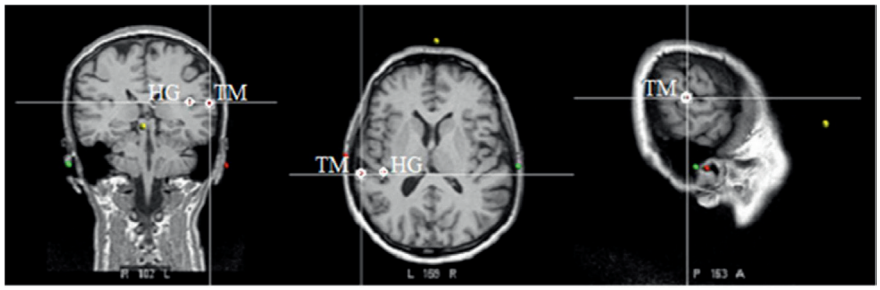
descripton), we gradually moved forward using 0.5–1 cm steps to the more anterior stimulation points. Several stimulation targets were used on the STG, the most anterior being situated close to the posterior end of the sulcus centralis (for lower pitch tinnitus) and the most posterior being situated approximately 2 cm more posteriorly (for high pitch tinnitus).

In Study 2, the induced E-field on the stimulated cortex varied between 48–143 V/m between patients and sessions in the active group. The active rTMS treatment was initiated in the posterior part of the AC for 12/19 patients and was moved forward in 8 patients, as the serial treatment progressed. For lower pitch tinnitus, the treatment was initiated at the most anterior point or the middle in 7/19 patients and later was moved toward more posterior locations in 4 patients.

In Study 3, patients received 10 sessions of either neuronavigated rTMS (nrTMS) or non-navigated rTMS over 2 weeks (5 daily weekday sessions). Each session consisted of 4000 pulses at a continuous 1 Hz rate given to the left STG/AC at 100% of the RMT. The actively induced current flow direction was directed downward due to coil technical reasons. All patients received 10 full sessions, except for 2 patients in the navigated group for whom one session was 3950 or 3980 pulses (due to technical problems) and one patient in the non-navigated group for whom one session was only 3100 pulses (also due to technical problems). In the navigated group, the intensity was lowered to 90-60% for 13 patients in some of the rTMS sessions, and in the non-navigated group, from to 90-70% for 11 patients because of annoying facial contractions. There were no statistically significant differences between the two treatment groups for the median maximal or minimal intensities during the treatment sessions ($p=0.17$-0.97), except for the median maximal intensity during the first session; it was 90% (range 70-100%) in nrTMS and 100% (range 80-100%) in non-navigated rTMS ($p=0.012$).

Figure 7 presents the coil localization with the Visor2 navigation system for the neuronavigated rTMS group in Study 3. First, the Heschl's Gyrus (HG) was determined from the patient's MRI dataset using the anatomical landmarks. Then the target marker (TM) was placed perpendicular to the HG on the surface of the 3D-model MRI of the brain (Figure 7a). During the first visit, a target stimulus (TS) was created. The coil was located so that the center-line of the coil was perpendicular to the STG and went through to the pre-defined TM, so that the induced electric field best stimulated the AC. The induced current flow direction for the first quarter cycle of the biphasic pulse pointed downward (the red arrow added in the figure) (Figure 7b). In each nrTMS treatment session, the coil was navigated to the position of TS with the help of the Reproduce stimuli function in the Visor2 (Figure 7c).

In Study 3, non-navigated "blind" rTMS treatment was based on the anatomical landmarks (the International 10-20 EEG electrode location system) and localization presented by (Langguth et al. 2006). First, the T3, C3, and Cz EEG electrode sites were defined according to this system. Then the coil was positioned by moving the coil 2.5 cm upwards from T3 on line T3-Cz and then 1.5 cm in the posterior direction perpendicularly to that line. Measurements of the EEG electrode locations and the navigation procedures were executed for both treatment groups to avoid any patient knowledge of the protocol.



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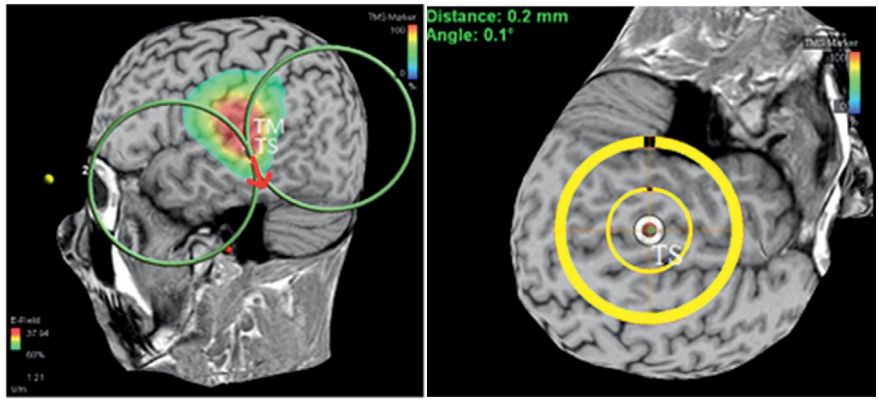


b. c.

Figure 7. The coil localization with the Visor2 navigation system for the neuronavigated rTMS (nrTMS) group in Study 3. See the text for more details. Reproduced with the permission of the copyright holders (Sahlsten et al. 2019).

4.5 Statistical analyses

The statistical analyses were performed using IBM SPSS statistics, Version 22 (SPSS Inc., Chicago, USA) (Studies 1 and 4) or the SAS System, Version 9.3 for Windows (SAS Institute Inc., Cary, USA) (Studies 1-3). All tests were performed as two-sided with the significance level set at 0.05.

4.5.1 Study 1

The descriptive statistics for tinnitus intensity and annoyance values were presented as mean and standard deviations (SD). Both intensity and annoyance were found to be normally distributed when tested using the Shapiro-Wilk test, and also by visual evaluation for each time point separately.

A hierarchical linear mixed-model (HLMM) with a compound symmetry covariance matrix was done. This repeated measures analysis of variance method assessed whether a change in the patients' self-reported ratings for tinnitus intensity or annoyance occurred during the consecutive treatment days. Only a time-effect describing effort within the patient change was used in the model with no other factors being included because of the small sample size. Additionally, post-hoc paired t-tests were conducted to evaluate the change in the perceived intensity and annoyance at the baseline and then at the end of the serial rTMS treatment. The Fisher's exact test was conducted to assess the influence of co-morbid conditions, such as depression, hearing loss, and chronic pain, to the rTMS treatment efficacy. The Spearman correlations were executed between intensity, annoyance, GIC score, and the total number of rTMS pulses, patient age, and the duration of symptoms.

4.5.2 Studies 2 and 3

The sample size calculations were based on the pilot study (Study 1) in which the mean change in tinnitus intensity was -2.6 (SD=1.4) measured using the NRS scale of 0–10. The placebo response (in Study 2) was estimated to be half of the mean change seen in the pilot study, being approximately -1.3. Selecting the statistical power at 80% and a significance level at 0.05 (two-tailed) led to a sample size of 19 per group.

All the data were presented as a mean with standard deviation (SD), or as a median with interquartile range (lower and upper quartiles) when describing the raw data, or as an estimated mean with standard error (SE) when describing the HLMM analysis results. Possible baseline differences were tested using the two-sample t-tests or a Wilcoxon rank sum test. Responders to rTMS were those patients who

showed at least a 30% reduction in tinnitus intensity, annoyance, or distress using the VAS scores at any assessment point, as this reduction is considered a clinically meaningful alleviation in the RCTs on pain (Dworkin et al. 2008). The reduction of 6 or more THI scores was considered as a minimal clinically relevant change (Zeman et al. 2011). An excellent responder was defined as having those reductions in all three VAS scores and the THI scores at any assessment point. At each time point, a comparison of the number of responders between the treatment groups was performed using the Fisher's exact test separately.

The normal distribution of variables was evaluated from the studentized residuals visually and then tested using the Shapiro–Wilk test. Logarithmic transformations were performed to THI (in Study 2), BDI and JSEQ to fulfil the normality assumption. To study whether the mean change in VAS scores (and additionally NRS intensity), THI, BDI and JSEQ occurred over the study period and whether the mean changes differed between the groups or not, the HLMM was used, including time as a within-factor, group as a between-factor, as well as their interaction effects. Additionally, the model included relevant clinical background factors (gender, presence of hearing deficit, use of medications for the central nervous system, location and duration of tinnitus, age group, smoking, depression, THI grading in Study 2 and gender, THI grading, duration of tinnitus, and age group: <50, 50-60, >60 years in Study 3).

From the final analysis model, all non-significant factors ($p>0.10$) were removed. However, the same final model for all VAS scores was conducted and a randomized treatment group was kept in the model even though it was not significant. The time factor was handled as categorical to be able to estimate all possible shapes of the mean changes over time. Compound symmetry covariance structure was used for time. Adjusted mean (SAS least square means) values with a 95% confidence interval (CI) were determined from the final model, including degrees of freedom together with F values (F_{df}) for all main results from the final model. If the normality assumption was not met, then the treatment groups were compared with the Wilcoxon rank sum test at each visit, and the Friedman's test was used to study the time effect for the entire study population.

Further still, to evaluate whether the baseline VAS scores were associated with the treatment effect, another model was built up in which the baseline was handled as a covariate (instead of one time point) with the same background factors as used in the model explained above. In addition, to evaluate the effect size of the study results, treatment efficacy was calculated using Cohen's *d* values (with 95% CI) at all follow-up time points compared against the baseline scores.

4.5.3 Study 4

All variables were analysed for normality by visually inspecting the data distribution and using the Shapiro-Wilk -test. Tinnitus intensity, annoyance, and distress were normally distributed; therefore, the mean and SD were reported. All other variables were not normally distributed, and thus, the median values and the first and the third quartiles were reported. The exact 95% CIs for the binomial distributions were obtained from the literature. The associations between the categorical variables were cross-tabulated and evaluated, using the two-sided Fisher's exact test. To achieve this goal, the tinnitus intensity was divided into categories where a score of 0–40 represented mild, >40–70 moderate, and >70–100 indicated severe tinnitus.

4.6 Ethical considerations

All four studies were performed according to the Declaration of Helsinki. Study 1 was a clinical patient case series study. In Study 1, information concerning the study was given to all patients. They all gave their informed spoken consent; attending the study was completely voluntary, and the patients were free to discontinue the treatment at any time. Studies 2-4 were approved by the Ethics Committee of the Intermunicipal Hospital District of Southwest Finland, and all patients in these studies gave their written informed consent.

5 RESULTS

5.1 Study 1

The mean intensity of tinnitus (measured using NRS) decreased during the rTMS treatment ($F(5,59) = 10.13$, $p<0.0001$). The mean intensity at the baseline was 7.1 (SD 1.8), and 4.5 (SD 2.2) after the serial treatment ($p<0.0001$). The intensity reduced on average by 39% (95% CI from -53% to -25%). Likewise, the mean annoyance caused by tinnitus (measured using NRS) decreased during the treatment ($F(5,59) = 8.19$, $p<0.0001$). The mean tinnitus related annoyance in daily life was 7.0 (SD 1.8) at the baseline, and 4.0 (SD 2.4) after the serial treatment ($p<0.0001$). The annoyance decreased on average 45% (95% CI from -60% to -29%). Of the patients, 8/13 (62%) experienced at least a 30% reduction in tinnitus intensity and 9/13 (69%) in tinnitus annoyance (Table 4).

Table 4. The results of Study 1 after the serial rTMS treatment. Modified from (Sahlsten et al. 2015).

Patient	Change (%) in tinnitus intensity	Change (%) in tinnitus annoyance	GIC	Change in tinnitus quality	Change in tinnitus location	Symptoms at follow-up (months)
1	-69	-75	+2	lower	moved to the right	2 - less than before
2	-23	-38	+2	softer	moved to the right	10 - increased
3	-37	-29	+1	creaker	moved more to the right	7 - still annoying
4	-40	-100	+2	diverse into lower tunes/disappear	centralized	6 - have returned
5	-33	-33	+1	milder	moved to the right	15 - still annoying
6	-26	-11	+1	lower and milder	moved slightly to the right	3 - still annoying
7	-20	-20	0	slightly milder	no change	3 - still annoying
8	-43	-43	+1	higher and milder	no change	2 - still annoying
9	-60	-67	+2	higher and milder	moved slightly to the right	no data
10	-13	-38	-	slightly lower and milder	moved slightly to the right	9 - still annoying
11	0	-17	0	slightly lower	no change	4 - still annoying
12	-80	-50	+2	milder	no change	6 - less than before
13	-63	-63	+2	lower	no change	6 - less than before

GIC = Global Impression of Change, scale -3 - +3 (for patient number 10, the data was missing)

All individual NRS values for tinnitus intensity and annoyance before the rTMS treatment, after the first four rTMS sessions and at the end of the treatment, are presented in Figure 8. The mixed model estimated means are additionally shown as thicker red lines. The patients evaluated their tinnitus in the evening after the treatment session (tinnitus diary); yet in some patients (numbers 2, 4, 5, and 6) one or two of the evening values were missing, and therefore, the NRS values immediately after the rTMS session were used instead. The mean tinnitus intensity

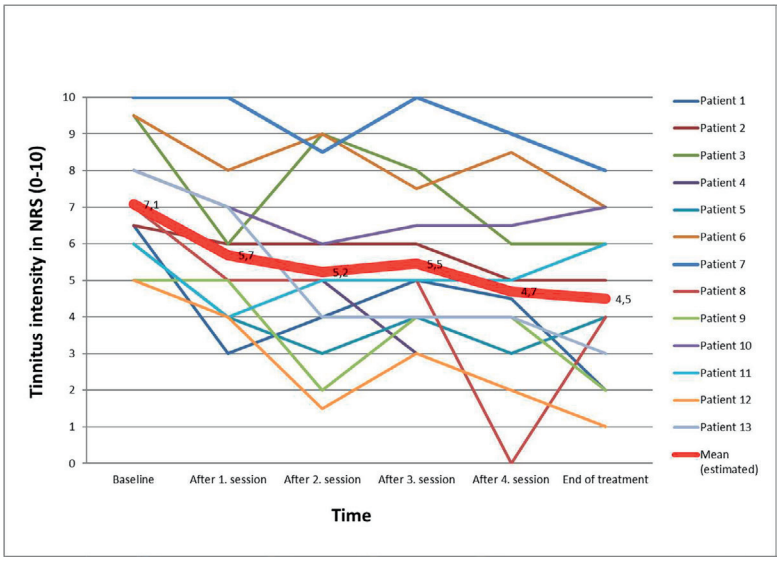
and annoyance reduced, starting immediately after the first rTMS session; thereafter, the reduction was continuous and rather linear. Figure 9 presents the decreasing trend of the individual ratings of tinnitus intensity and annoyance from the baseline to the end of the serial treatments.

In addition to intensity and annoyance, the rTMS treatment influenced the location and the pitch of tinnitus. Of the patients, 7/13 noted that their bilateral tinnitus had lateralized to the right after the serial rTMS was given to the left STG (Table 4). Further, 10/13 patients reported that their tinnitus sound had changed. This change varied among the patients; the tinnitus was altered into lower, softer, or sharper sounds, or broke down into different spectral components with a lower intensity (Table 4).

According to the GIC scale, 10/13 (77%) patients felt they had benefitted from the treatment; 6 patients reported GIC +2, and 4 patients reported GIC +1 (Table 4, Figure 10). Two patients reported no benefit from the treatment (GIC 0), although they had a slight reduction in tinnitus intensity or annoyance according to their NRS values. For one patient, the GIC was missing, but he also had a mild decrease in tinnitus intensity and a significant (30%) decrease in tinnitus annoyance according to the NRS values (Table 4). The tinnitus did not worsen in any of the patients.

The duration of tinnitus, the age or gender of the patients, or the total number of TMS pulses given were not significantly associated with the efficacy of the treatment. Further, co-morbidities (depression, chronic pain, and hearing loss) did not seem to influence the results of the treatment.

Short-term, later follow-up information was received from 5 patients, and they reported that the full effect of the treatment had lasted from 2 days up to 6 days. Long-term treatment effects were collected from the patient archives where available. After 2-15 months, 12 patients still had tinnitus (Table 4). Among those, one patient reported more intense tinnitus symptoms, and 3 patients felt the tinnitus was less severe than before the treatment, in two of those three, at 6 months after rTMS. For one patient, no long-term data was found.



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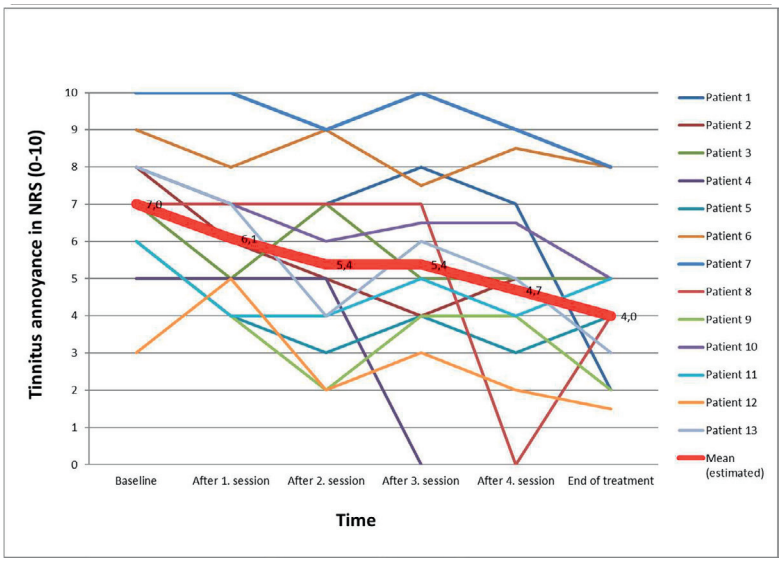

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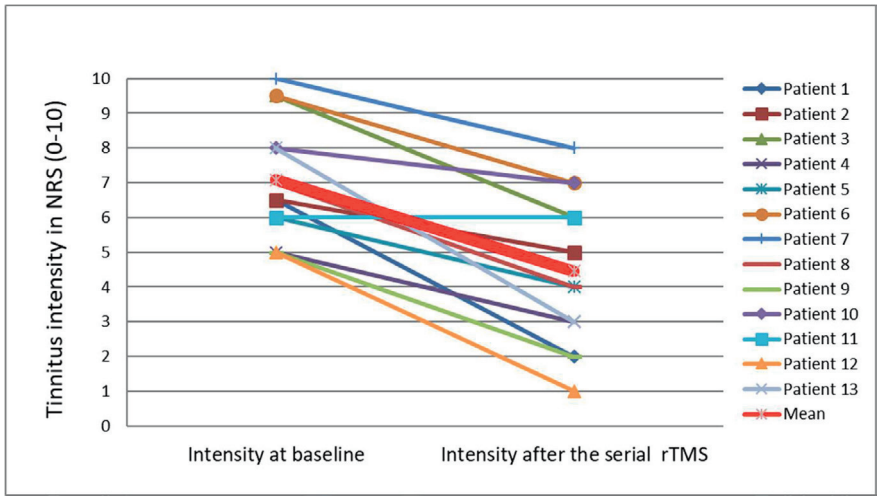
Figure 8. The effect of rTMS on patient self-rated tinnitus intensity (a) and annoyance (b) as the value for the eleven-point NRS (0-10) at the baseline, after the first four rTMS sessions, and at the end of the serial rTMS treatment. The estimated mean values from the repeated measures ANOVA statistical model are shown as a thick red line (SE for intensity 0.61 and 0.64 for annoyance). Reproduced with the permission of the copyright holders (Sahlsten et al. 2015).



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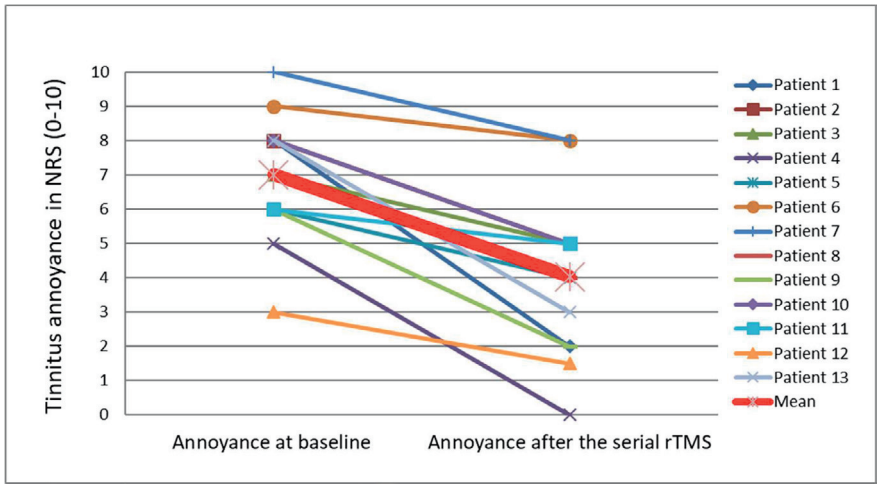

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Figure 9. The effect of rTMS on patient self-rated tinnitus intensity (a) and annoyance (b) in NRS values (0-10) at the baseline and after the serial rTMS treatment. Reproduced with the permission of the copyright holders (Sahlsten et al. 2015).

There were no major side effects, such as seizures, but mild side effects were encountered in 4/13 patients. The stimulation intensity was lowered from 110-100% to 90% in 3 patients because of painful facial muscle contractions occurring during the stimulation, after which these patients were able to continue the treatment. Further, one patient noticed that her migraine worsened during the treatment, so she discontinued the treatment after 8 sessions. In one patient, the active E-field was directed downward during the first session, causing slight hypomanic symptoms in that patient during the treatment day.

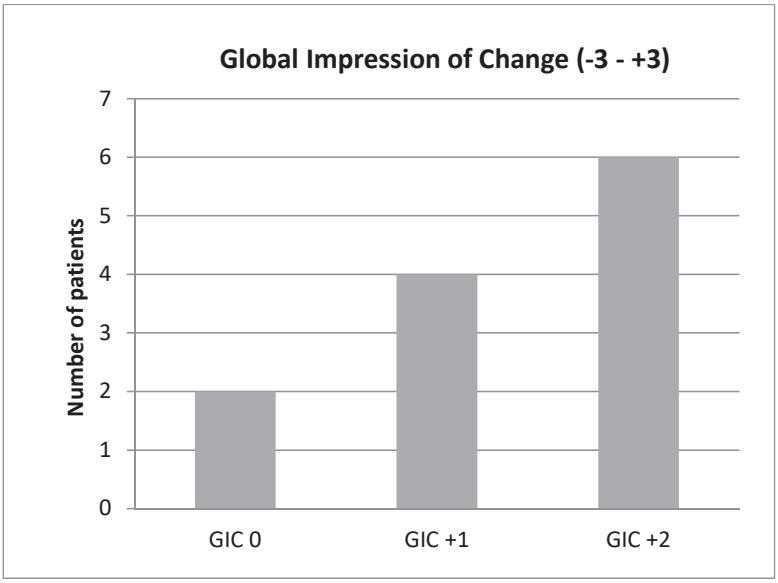


Figure 10. The Global Impression of Change (GIC) values reported by the patients after the serial rTMS. The GIC value was missing for one patient.

Clinical vignette

Patient number 13 was a 59-year-old man, who in addition to tinnitus had multiple sclerosis, left spastic hemiparesis, and central neuropathic pain (face, and upper and lower extremities on the left side). He had suffered from bilateral high pitch tinnitus and high frequency sensorineural hearing loss for 6 years. All conditions were chronic, severe, disabling, and treatment resistant. At the baseline, the patient rated his tinnitus intensity at 8, annoyance at 8, and pain intensity at 9, interference at 8 using NRS (0-10). After the first week of the treatment (5 sessions) his tinnitus intensity and annoyance had reduced to 4 and 4, and the pain had vanished (NRS 0). In addition, his spasticity was better. After the serial treatment (9 sessions), this patient rated his tinnitus as 3 and 3 and his GIC value as +2. Further, his pain and spasticity were absent, and he had been able to discontinue neuropathic pain and muscle-relaxing medications. He also experienced an improvement in his sleep. After 6 months, he rated his tinnitus intensity as 6 and his annoyance as 5 on the NRS scale. His pain intensity (NRS 3) and spasticity (NRS 1) were still almost absent, and he was able to continue without medications, with only physiotherapy.

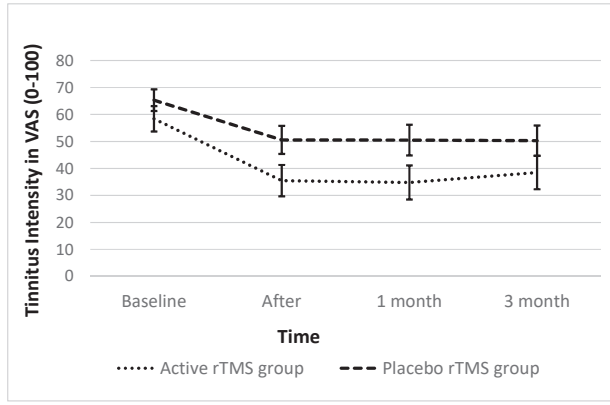
5.2 Study 2

5.2.1 Primary outcome measures

Overall, a significant reduction over 3 months was detected in mean tinnitus intensity (HLMM: F_3=15.7, p<0.0001), annoyance (F_3=8.8, p<0.0002) and distress (F_3=9.1, p<0.0002) VAS scores in the entire study population. Nevertheless, no significant differences existed between the active and placebo group over time (F_3=0.8, p=0.50 for intensity, F_3=0.3, p=0.82 for annoyance, F_3=0.9, p=0.46 for distress (Figure 11, Table 5). Therefore, post hoc paired comparisons could not be done even though the tinnitus intensity was lower in the active group immediately after the treatment and at the 1-month control (Figure 11 a). In both groups, there was an improvement in the VAS scores (intensity, annoyance, and distress) immediately after the treatment and, also at the 1- and 3-month controls. The mean tinnitus intensity in the NRS scores was reduced to 5.8 (SE 0.4) at 6 months compared to the baseline (the first telephone interview) of 6.8 (SE 0.3) (F_1=14.2, p=0.0006), but again, there was no significant difference between the groups (F_1=4.0, p=0.053).

In the active group, the effect size calculated in Cohen's *d* for tinnitus intensity between the baseline and post-treatment time points ranged from 0.92 (95% CI 0.35–1.48) immediately after rTMS to 0.82 (95% CI 0.32–1.33) at 3 months. In the placebo group, the effect size was also rather high, ranging from 0.69 (95% CI 0.18–1.19) immediately after rTMS to 0.78 (95% CI 0.32–1.24) at 3 months. The baseline VAS scores were not associated with rTMS treatment efficacy (p=0.86 for intensity and distress, p=0.33 for annoyance). A patient's gender, hearing loss, use of the central nervous system affecting medication (depression medication excluded), and the location or duration of tinnitus were not associated with the treatment results (all p values >0.10; thus, these factors were excluded from the final statistical model). The duration of tinnitus was associated with tinnitus annoyance and distress; the longer the duration of tinnitus, the higher the VAS scores were (p=0.011 for both annoyance and distress). Older patients (age group >60 years) benefitted more from the treatment than did the younger patients for tinnitus intensity and similarly in both the active and placebo groups (p=0.0013).

There was a significant decrease (F_4=13.8, p<0.0001) in the THI scores in the whole group over time with no significant difference between the two treatment groups (F_4=1.3, p=0.28) (Figure 12, Table 6). The decrease in the median THI scores (from 30 to 12) persisted for up to 6 months (HLMM: A comparison between the baseline and 6 months p<0.0001). The change in the THI scores was associated with depression in both groups, as depressed patients experienced less of a decrease (F_4=4.1, p=0.0035).



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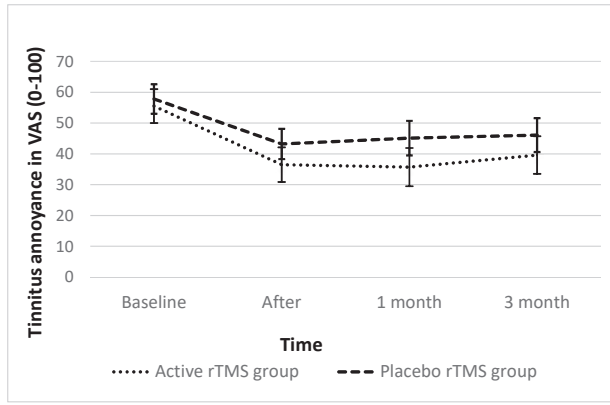

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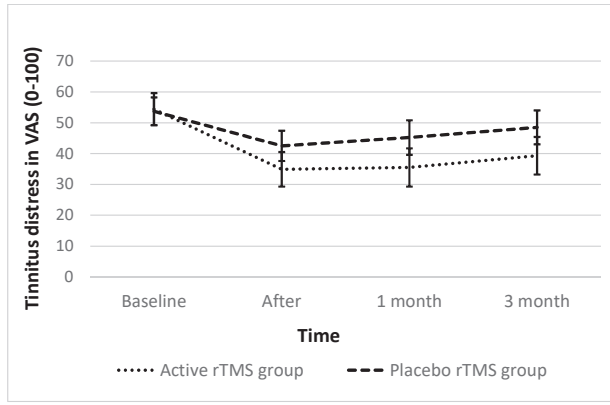


c.

Figure 11. The effect of the serial rTMS treatment on patients' self-rated tinnitus (a) intensity, (b) annoyance, and (c) distress in the active rTMS and placebo group on the Visual Analog Scale (VAS 0–100), in terms of time from the beginning of the treatment, the adjusted means (±SE). Reproduced with the permission of the copyright holders (Sahlsten et al. 2017).

Table 5. Tinnitus (a) intensity, (b) annoyance, and (c) distress on the Visual Analog Scale (VAS 0-100) in terms of time from the beginning of the rTMS treatment, adjusted mean, SE. Reproduced with the permission of the copyright holders, supplementary material (Sahlsten et al. 2017).

a. Tinnitus intensity

Time	Total group	SE	P value	Active rTMS group	SE	Placebo rTMS group	SE	P value (between-group)
Baseline	61.8	3.7		58.4	4.7	65.3	4.0	0.23
After	43.0	4.4		35.5	5.8	50.6	5.2	
1 month	42.6	4.7	<0.0001 over time	34.8	6.3	50.5	5.7	0.50 over time
3 month	44.4	4.6		38.5	6.2	50.3	5.6	

b. Tinnitus annoyance

Time	Total group	SE	P value	Active rTMS group	SE	Placebo rTMS group	SE	P value (between-group)
Baseline	56.6	4.3		55.5	5.5	57.8	4.8	0.87
After	39.9	4.3		36.5	5.6	43.2	4.9	
1 month	40.4	4.7	0.0002 over time	35.7	6.2	45.1	5.6	0.82 over time
3 month	42.9	4.7		39.6	6.1	46.1	5.5	

c. Tinnitus distress

Time	Total group	SE	P value	Active rTMS group	SE	Placebo rTMS group	SE	P value (between-group)
Baseline	54.0	4.1		54.4	5.2	53.7	4.5	0.47
After	38.7	4.3		34.9	5.6	42.5	4.9	
1 month	40.3	4.7	0.0002 over time	35.5	6.2	45.2	5.6	0.46 over time
3 month	43.9	4.7		39.3	6.1	48.5	5.5	

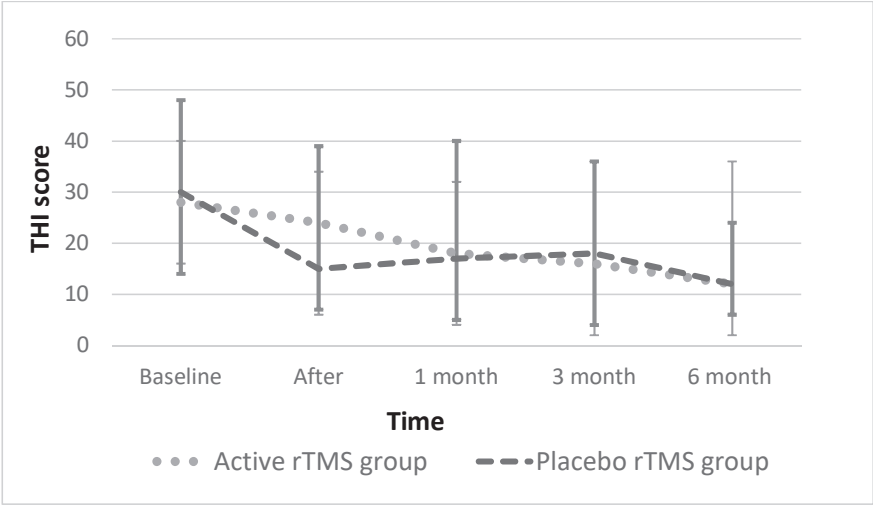


Figure 12. The effect of the serial rTMS treatment on the median Tinnitus Handicap Inventory (THI) scores (± quartiles) in the active rTMS and placebo group in terms of time from the beginning of the treatment. See Table 6 for details. Reproduced with the permission of the copyright holders (Sahlsten et al. 2017).

Table 6. Tinnitus Handicap Inventory (THI) scores in terms of time from the beginning of the rTMS treatment, median, lower, and upper quartiles. Reproduced with the permission of the copyright holders, supplementary material (Sahlsten et al. 2017).

Time	Total group	Quartiles	P value	Active rTMS	Quartiles	Placebo rTMS	Quartiles	P value (between-group)
Baseline	30	14 - 44		28	16 - 40	30	14 - 48	0.68
After	18	6 - 34		24	6 - 34	15	7 - 39	
1 month	18	4 - 38	<0.0001 over time	18	4 - 32	17	5 - 40	0.28 over time
3 month	16	4 - 36		16	2 - 36	18	4 - 36	
6 month	12	4 - 30		12	2 - 36	12	6 - 24	

Although there were more excellent responders (clinically notable decreases for all VAS and THI scores) in the active group at all time points, the difference for the placebo group remained non-significant (Figure 13, Table 7a). Considering at least a 30% decrease in tinnitus intensity after rTMS as a response, resulted in 53% responders in the active group and 30% in the placebo group (p=0.20), whereas using at least a 6-point decrease in the THI scores resulted in 58% and 65% responders (p=0.75), respectively (Table 7c and 7d).

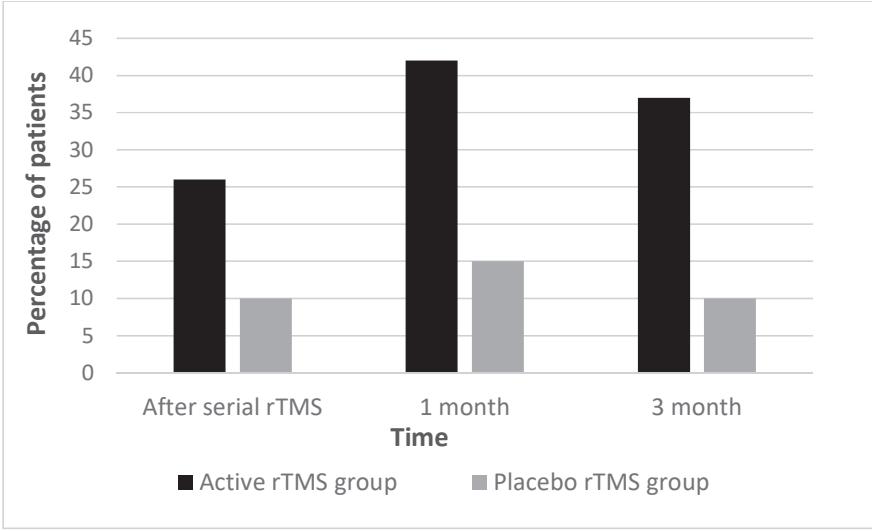


Figure 13. The percentage of the excellent responders in the active rTMS and placebo group are shown here in terms of time from the beginning of the treatment. See Table 7a for details. Reproduced with the permission of the copyright holders, supplementary material (Sahlsten et al. 2017).

Table 7. The percentage of the responders to rTMS (and the number of patients) in terms of time from the beginning of the treatment: (a) the excellent responders based on the reduction of tinnitus Visual Analog Scale (VAS) score (intensity, annoyance, and distress) ≥30% and the reduction of Tinnitus Handicap Inventory (THI) scores ≥6, (b) the responders based on the reduction of tinnitus VAS score (intensity, annoyance, and distress) ≥30%, (c) the responders based only on the reduction of tinnitus intensity (VAS) ≥30 % and (d) the responders based only on the reduction of THI scores ≥6, compared with the baseline. Reproduced with the permission of the copyright holders, supplementary material (Sahlsten et al. 2017).

a.

Time	Active rTMS group, % (no. of patients)	Placebo rTMS group, % (no. of patients)	P value (between-group)
After	26 (5)	10 (2)	0.24
1 month	42 (8)	15 (3)	0.082
3 month	37 (7)	10 (2)	0.065

b.

Time	Active rTMS group, % (no. of patients)	Placebo rTMS group, % (no. of patients)	P value (between-group)
After	42 (8)	15 (3)	0.082
1 month	47 (9)	25 (5)	0.19
3 month	37 (7)	20 (4)	0.30

c.

Time	Active rTMS group, % (no. of patients)	Placebo rTMS group, % (no. of patients)	P value (between-group)
After	53 (10)	30 (6)	0.20
1 month	53 (10)	30 (6)	0.20
3 month	47 (9)	35 (7)	0.52

d.

Time	Active rTMS group, % (no. of patients)	Placebo rTMS group, % (no. of patients)	P value (between-group)
After	58 (11)	65 (13)	0.75
1 month	74 (14)	60 (12)	0.50
3 month	68 (13)	60 (12)	0.74
6 month	79 (15)	70 (14)	0.72

Based on the GIC scale, 5/19 (26%) of the patients in the active group and only 1 (5%) patient in the placebo group felt they had benefitted (GIC ≥ +1) from the treatment after the serial rTMS (Figure 14). At 6-month control 4/19 (21%) of the patients still reported a positive GIC in the active group. Further, only a few patients reported a negative GIC; 2/19 (11%) reported GIC -1 in the active group and 1/20 (5%) reported GIC -2 in the placebo group after rTMS.

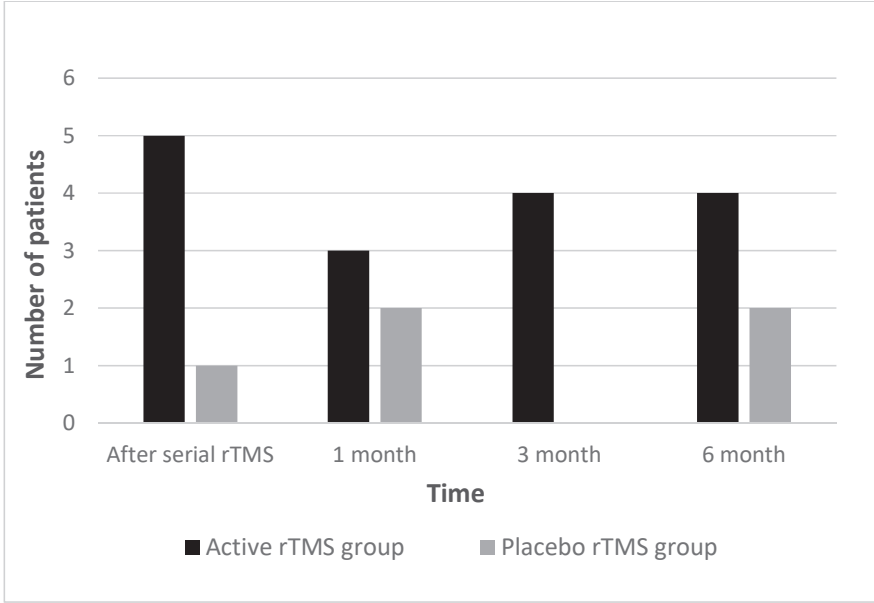


Figure 14. The number of patients who felt they had benefitted from the treatment, based on the Global Impression of Change (GIC) scale (≥+1) in terms of the time from the beginning of the rTMS treatment. Reproduced with the permission of the copyright holders, supplementary material (Sahlsten et al. 2017).

5.2.2 Secondary outcome measures and other findings

There were no changes in hearing in the whole group or between the groups in either ear after rTMS (Table 8a). No changes were found in psycho-acoustically measured loudness or the pitch of tinnitus in the whole group or between the groups during the 3-month follow-up time (Tables 8b and 8c).

Table 8. The results in (a) hearing (pure tone average (PTA) of 0.5, 1, 2, and 4 kHz of individual audiograms) in Decibels (dB), (b) psycho-acoustically measured loudness of tinnitus in dB and (c) pitch of tinnitus in kHz, measured in terms of time from the beginning of the rTMS treatment, mean (SD) (a, b) and median (min-max) (c), R= Right ear, L= Left ear. Reproduced with the permission of the copyright holders, supplementary material (Sahlsten et al. 2017).

a. Hearing level (dB)

Time	Active rTMS group, R/L	Placebo rTMS group, R/L	P value (between-group), R/L	P value (total group), R/L
Baseline	14.0(11.5)/18.5(19.8)	16.0(12.6)/18.5(12.7)	0.46/0.98	
After	13.7(11.4)/18.5(20.5)	16.3(13.3)/18.7(13.0)	0.37/0.84	0.92/0.65

b. Tinnitus loudness (dB)

Time	Active rTMS group, R/L	Placebo rTMS group, R/L	P value (between-group), R/L	P value (total group), R/L
Baseline	34.2(21.9)/24.5(26.1)	26.1(23.0)/43.9(26.9)	0.27/0.03	
After	29.7(24.4)/25.8(27.2)	23.7(21.5)/40.8(20.7)	0.09/0.83 over time	0.52/0.33 over time
1 month	29.2(22.2)/28.7(26.7)	28.7(25.3)/45.5(23.2)		
3 month	30.3(22.1)/27.5(26.2)	28.2(25.1)/46.0(24.8)		

c. Tinnitus pitch (kHz)

Time	Active rTMS group, R/L	Placebo rTMS group, R/L	P value (between-group), R/L	P value (total group), R/L
Baseline	6(3-8)/6(1-8)	4(0.5-8)/6(0.5-8)	0.098/0.50	
After	6(3-8)/7(1-8)	6(1-8)/6(1-8)	0.60/0.57	0.18/0.58 over time
1 month	8(3-8)/6(1-8)	6(1-8)/6(0.5-8)	0.12/0.94	
3 month	6(3-8)/6(1-8)	6(0.5-8)/6(1-8)	0.45/0.80	

A minor improvement was detected in the BDI and JSEQ scores after rTMS for the whole group and in both treatment groups (HLMM: time effect BDI: F_2=16.8, p<0.0001, JSEQ: F_2=5.5, p=0.0062), with no significant differences between the groups over time (Table 9).

Table 9. Beck Depression Inventory (BDI) scores (a) and Jenkins Sleep Evaluation Questionnaire (JSEQ) scores (b) in terms of time from the beginning of the rTMS treatment, median (lower and upper quartiles). Reproduced with the permission of the copyright holders, supplementary material (Sahlsten et al. 2017).

a. BDI

Time	Active rTMS group	Placebo rTMS group	P value (between-group)	P value (time-effect total group)
Baseline	5.0 (2.0-9.0)	4.0 (0-10.5)	0.69	
After	2.0 (0-5.0)	1.0 (0-6.0)	0.52 over time	<0.0001 over time
3 month	3.0 (0-8.0)	2.0 (0-6.0)		

b. JSEQ

Time	Active rTMS group	Placebo rTMS group	P value (between-group)	P value (time-effect total group)
Baseline	8.0 (4.0-10.0)	4.5 (2.0-10.0)	0.80	
After	5.0 (2.0-10.0)	7.0 (2.0-9.0)	0.63 over time	0.0062 over time
3 month	7.0 (3.0-12.0)	5.0 (1.5-12.0)		

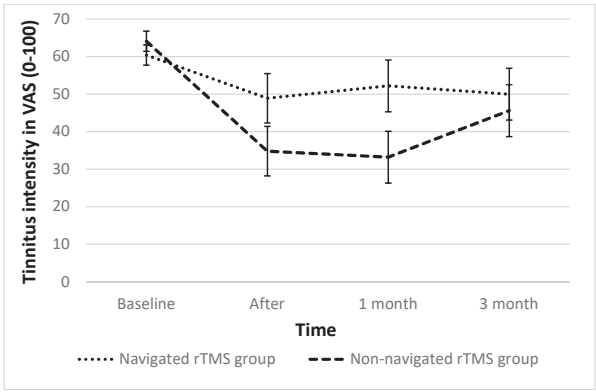
The patients were queried about their opinions of the treatment they had received after the last follow-up. In the active group, 9/19 (47%) patients guessed correctly about having received active rTMS, and in the placebo group, 6/20 (30%) thought they had received active rTMS.

There were no major or permanent side effects, but some patients did report local irritation due to muscle twitching at the region of the stimulation side and, also minor temporary side effects like headaches.

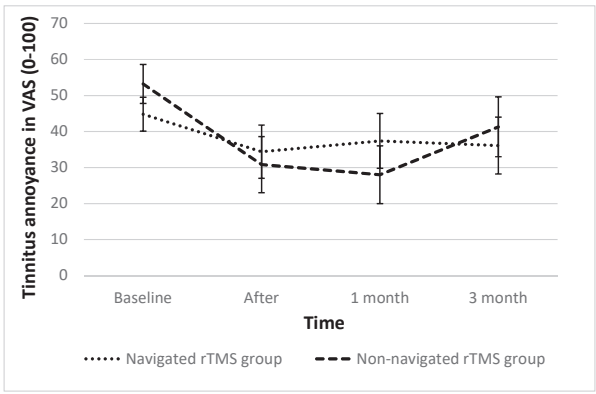
5.3 Study 3

5.3.1 Primary outcome measures

Overall, a reduction in VAS scores over 3 months was detected in mean tinnitus intensity (HLMM: F_3=7.34, p=0.0006), annoyance (F_3=4.45, p=0.0093) and distress (F_3=5.04, p=0.0051) in the entire study group. The only difference between the navigated and the non-navigated group was in tinnitus intensity (F_3=2.96, p=0.0451), thereby favoring the non-navigated rTMS, while no such differences in tinnitus annoyance (F_3=2.04, p=0.13) or distress (F_3=1.65, p=0.19) were observed (Figure 15, Table 10). The VAS scores (intensity, annoyance, and distress) reduced immediately after the serial treatment and stayed at a lower level for up to the 1- and 3-month controls in both groups. The mean tinnitus intensity in NRS scores reduced in the non-navigated group from 6.5 (SD 1.4) at the baseline (the first telephone interview) to 5.6 (SD 2.3) at the 6-month control, whereas in the navigated group the scores returned to the baseline level from, 5.9 (SD 1.2) to 6.1 (SD 1.8). A difference was observed between the mean changes over time between the groups and favored the non-navigated rTMS (F_1=5.46, p=0.0253).



a.



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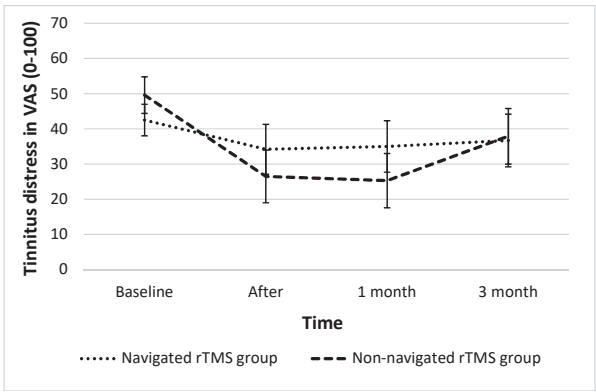

c.

Figure 15. The effect of neuronavigated and non-navigated serial rTMS treatment on the patient's self-rated tinnitus (a) intensity, (b) annoyance, and (c) distress in Visual Analog Scale (VAS 0-100) in terms of time from the beginning of the treatment, the adjusted means (±SE). See Table 10 for more details. Reproduced with the permission of the copyright holders (Sahlsten et al. 2019).

Table 10. Tinnitus (a) intensity, (b) annoyance, and (c) distress on the Visual Analog Scale (VAS 0-100) in terms of time from the beginning of the rTMS treatment, adjusted mean, SE. Reproduced with the permission of the copyright holders (Sahlsten et al. 2019).

a. Tinnitus intensity

Time	Total group	SE	P value	Navigated rTMS group	SE	Non-navigated rTMS group	SE	P value (between-group)
Baseline	62.2	1.9		60.4	2.7	64.1	2.7	0.24
After	41.9	4.7		48.9	6.6	34.8	6.6	
1 month	42.7	4.9	0.0006 over time	52.2	6.9	33.2	6.9	0.0451 over time
3 month	47.8	4.9		50.0	6.9	45.6	6.9	

b. Tinnitus annoyance

Time	Total group	SE	P value	Navigated rTMS group	SE	Non-navigated rTMS group	SE	P value (between-group)
Baseline	49.0	3.9		44.8	4.7	53.2	5.4	0.59
After	32.6	5.6		34.4	7.4	30.8	7.8	
1 month	32.7	5.7	0.0093 over time	37.4	7.6	28.0	8.0	0.13 over time
3 month	38.7	5.9		36.1	7.9	41.3	8.3	

c. Tinnitus distress

Time	Total group	SE	P value	Navigated rTMS group	SE	Non-navigated rTMS group	SE	P value (between-group)
Baseline	46.0	3.7		42.5	4.5	49.6	5.2	0.38
After	30.4	5.4		34.2	7.1	26.5	7.5	
1 month	30.1	5.5	0.0051 over time	35.0	7.3	25.3	7.7	0.19 over time
3 month	37.3	5.6		36.7	7.5	37.9	7.9	

A decrease in the THI scores for the whole group over time was observed (F_4=17.30, p<0.0001). However, there were no differences between the two treatment groups (F_4=0.14, p=0.97) (Figure 16, Table 11). In fact, the groups showed surprisingly similar changes in time after rTMS. The decrease in the mean THI scores (from 34 to 13) was clinically significant and was also maintained for up to 6 months.

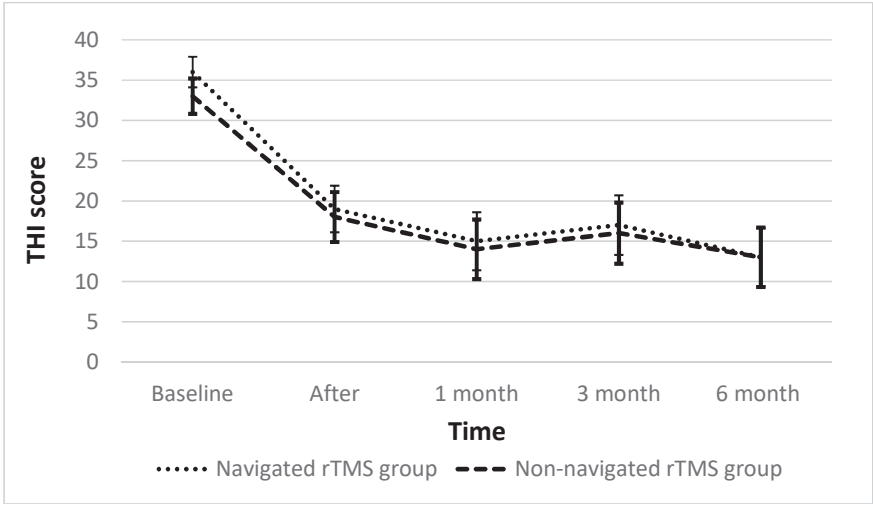

Figure 16. The effect of neuronavigated and non-navigated serial rTMS treatment on the Tinnitus Handicap Inventory (THI) scores in terms of time from the beginning of the treatment, the adjusted means (±SE). See Table 11 for more details. Reproduced with the permission of the copyright holders (Sahlsten et al. 2019).

Table 11. Tinnitus Handicap Inventory (THI) scores in terms of time from the beginning of the rTMS treatment, adjusted mean, SE. Reproduced with the permission of the copyright holders (Sahlsten et al. 2019).

Time	Total group	SE	P value	Navigated rTMS group	SE	Non-navigated rTMS group	SE	P value (between-group)
Baseline	34	1.6		36	1.9	33	2.2	0.49
After	18	2.2		19	2.9	18	3.1	
1 month	14	2.7	<0.0001 over time	15	3.6	14	3.7	0.97 over time
3 month	16	2.7		17	3.7	16	3.8	
6 month	13	2.6		13	3.6	13	3.7	

The background variables, including gender, duration of tinnitus, grade of tinnitus (THI grade), and age group, were assessed in the statistical model. Gender had an effect, as women presented with higher tinnitus intensity than men did (F1=5.8, p=0.022). Overall, a longer duration of tinnitus and a lower THI grade were associated with less tinnitus annoyance (F_1=6.2, p=0.018, F_4=4.0, p=0.010), respectively. For distress, the only significant background variable was the THI grade (F_4=4.0, p=0.010); the higher THI grade was associated with more distressing symptoms.

The effect size was calculated in Cohen's *d* for tinnitus intensity between the baseline and the post-treatment time points and ranged between 0.33-0.47 after nrTMS and between 0.55-1.07 after non-navigated rTMS. See Table 12 for details and the Cohen's *d* values for the different variables.

Table 12. The effect size in Cohen's *d* (with 95% CI) for tinnitus (a) intensity, (b) annoyance, and (c) distress (measured in Visual Analog Scale (VAS) 0-100), as calculated between the baseline and post-treatment time points. Reproduced with the permission of the copyright holders (Sahlsten et al. 2019).

a. Intensity

Time	Navigated rTMS group	95% CI	Non-navigated rTMS group	95% CI
After	0.38	0.19-0.95	1.07	0.44-1.69
1 month	0.33	0.06-0.73	1.02	0.40-1.65
3 month	0.47	0.07-0.87	0.55	0.006-1.11

b. Annoyance

Time	Navigated rTMS group	95% CI	Non-navigated rTMS group	95% CI
After	0.35	0.15-0.85	0.75	0.14-1.36
1 month	0.26	0.19-0.71	0.81	0.21-1.42
3 month	0.31	0.21-0.83	0.37	0.15-0.88

c. Distress

Time	Navigated rTMS group	95% CI	Non-navigated rTMS group	95% CI
After	0.29	0.19-0.77	0.83	0.23-1.42
1 month	0.31	0.06-0.68	0.78	0.18-1.38
3 month	0.25	0.16-0.67	0.37	0.16-0.90

There was no significant difference in the rate of excellent responders (a clinically notable decrease in all the VAS and THI scores) between the navigated and the non-navigated groups; however, there were more excellent responders in the non-navigated group, especially at the 1-month control (55% vs. 25%, Fisher's exact test p=0.11) (Figure 17, Table 13a). Further, no significant differences were observed in other responder rates either (see Table 13 for details). Using at least a 6-point decrease in the THI scores produced similar responder rates in both groups, i.e., 75% responders in the navigated and 80% in the non-navigated group immediately after the serial rTMS (p=1.00) (Table 13d).

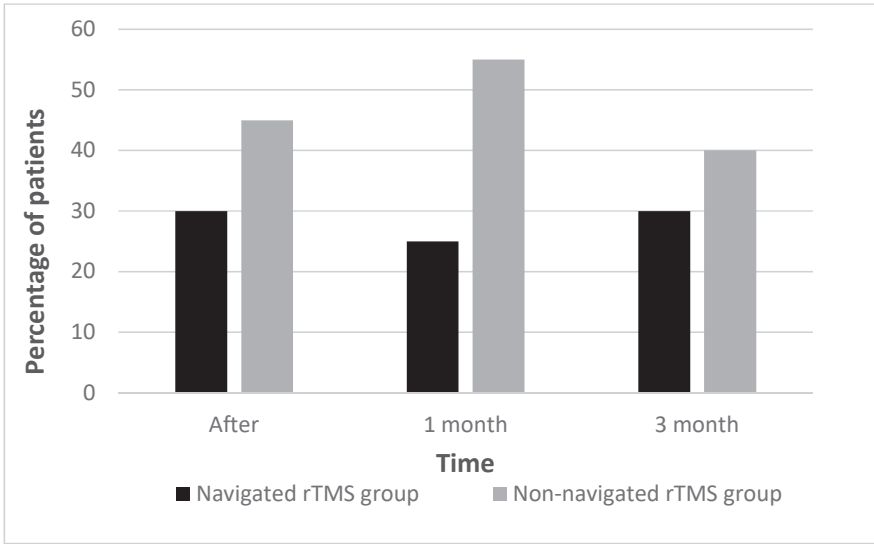

Figure 17. The percentage of excellent responders in the navigated rTMS and non-navigated group are shown in terms of time from the beginning of the treatment. See Table 13a for details. Reproduced with the permission of the copyright holders, supplementary material (Sahlsten et al. 2019).

Based on the GIC scale alone, 8/20 (40%) of patients in the navigated group and 3/20 (15%) in the non-navigated group benefitted from the rTMS treatment (GIC ≥ +1) (Figure 18). Further, only a few patients reported negative GIC: 1/20 (5%) reported GIC -1 in the navigated group, and 3/20 (15%) reported GIC -1 in the non-navigated group after rTMS. The groups did not differ (p-values 0.52-0.87) in their GIC values (-3 - +3) at different evaluation points.

Table 13. The percentage of the responders to rTMS (and the number of the patients) in terms of time from the beginning of the treatment: (a) the excellent responders based on the reduction of tinnitus Visual Analog Scale (VAS) score (intensity, annoyance, and distress) ≥30% and the reduction of Tinnitus Handicap Inventory (THI) scores ≥6, (b) the responders based on the reduction of tinnitus VAS score (intensity, annoyance and distress) ≥30%; (c) the responders based only on the reduction of tinnitus intensity (VAS) ≥30%; and (d) the responders based only on the reduction of THI scores ≥6, compared to the baseline. Reproduced with the permission of the copyright holders, supplementary material (Sahlsten et al. 2019).

a.

Time	Navigated rTMS group, % (no. of patients)	Non-navigated rTMS group, % (no. of patients)	P value (between-group)
After	30 (6)	45 (9)	0.51
1 month	25 (5)	55 (11)	0.11
3 month	30 (6)	40 (8)	0.74

b.

Time	Navigated rTMS group, % (no. of patients)	Non-navigated rTMS group, % (no. of patients)	P value (between-group)
After	45 (9)	55 (11)	0.75
1 month	35 (7)	65 (13)	0.11
3 month	35 (7)	50 (10)	0.52

c.

Time	Navigated rTMS group, % (no. of patients)	Non-navigated rTMS group, % (no. of patients)	P value (between-group)
After	45 (9)	65 (13)	0.34
1 month	40 (8)	75 (15)	0.054
3 month	35 (7)	55 (11)	0.34

d.

Time	Navigated rTMS group, % (no. of patients)	Non-navigated rTMS group, % (no. of patients)	P value (between-group)
After	75 (15)	80 (16)	1.00
1 month	70 (14)	85 (17)	0.45
3 month	70 (14)	80 (16)	0.72
6 month	85 (17)	85 (17)	1.00

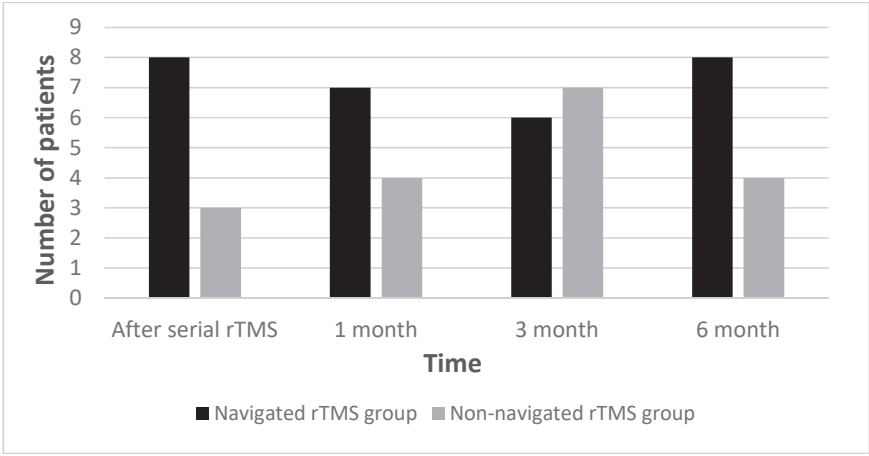

Figure 18. The number of patients who felt they had benefitted from the treatment, based on the Global Impression of Change (GIC) scale (≥+1) in time from the beginning of the rTMS treatment. Reproduced with the permission of the copyright holders, supplementary material (Sahlsten et al. 2019).

5.3.2 Secondary outcome measures and other findings

There were no changes in hearing for the entire group or between the groups for either ear after rTMS (Table 14a). There was a reduction in the psycho-acoustically measured loudness of tinnitus (dB) in the left ear for the whole group (mean values; baseline 42.7 (SD 21.0) and the 1-month control 24.4 (SD 21.7), p=0.0023 over time); otherwise, during the follow-up, no changes were observed in loudness or the pitch of tinnitus for the whole group or between the groups (Table 14b and 14c).

Table 14. The results in (a) hearing (pure tone average of 0.5, 1, 2, and 4 kHz for individual audiograms) in Decibels, (b) psycho-acoustically measured loudness of tinnitus in Decibels, and (c) pitch of tinnitus in kHz, measured in terms of time from the beginning of the rTMS treatment, median (lower and upper quartiles). R= Right ear, L= Left ear. Reproduced with the permission of the copyright holders, supplementary material (Sahlsten et al. 2019).

a. Hearing level (dB)

Time	Navigated rTMS group, R/L	Non-navigated rTMS group, R/L	P value (between-group), R/L	P value (total group), R/L
Baseline	19.5 (11.0-29.5)/19.0 (8.0-27.5)	17.0 (7.0-28.0)/13.5 (6.0-26.5)	0.48/0.47	
After	21.0 (9.5-29.5)/15.5 (7.0-26.5)	14.5 (5.5-25.0)/14.5 (6.0-27.0)	0.32/0.92	0.13/0.30

b. Tinnitus loudness (dB)

Time	Navigated rTMS group, R/L	Non-navigated rTMS group, R/L	P value (between-group), R/L	P value (total group), R/L
Baseline	35.0 (20.0-45.0)/30.0 (20.0-52.5)	50.0 (30.0-65.0)/37.5 (20.0-50.0)	0.13/0.92	
After	21.3 (1.3-40.0)/5.0 (0-25.0)	37.5 (0-56.3)/25.0 (7.5-35.0)	0.41/0.089	0.57/0.0023 over time
1 month	20.0 (4.0-32.5)/25.0 (0-41.3)	10.0 (0-57.5)/22.5 (5.0-38.8)	0.84/0.66	
3 month	30.0 (15.0-45.0)/30.0 (25.0/45.0)	45.0 (25.0-65.0)/30.0 (15.0-42.5)	0.31/0.88	

c. Tinnitus pitch (kHz)

Time	Navigated rTMS group, R/L	Non-navigated rTMS group, R/L	P value (between-group), R/L	P value (total group), R/L
Baseline	6.0 (3.0-8.0)/6.0 (4.0-6.0)	8.0 (4.0-8.0)/6.0 (4.0-8.0)	0.38/0.97	
After	4.0 (0.25-6.5)/2.0 (0-6.0)	4.0 (1.0-8.0)/4.0 (1.0-8.0)	0.55/0.28	0.25/0.11 over time
1 month	4.0 (1.25-7.5)/4.0 (0-6.0)	5.0 (0-8.0)/4.0 (0.75-7.0)	0.98/0.68	
3 month	4.0 (3.0-6.0)/4.0 (4.0-8.0)	6.0 (2.0-8.0)/6.0 (4.0-8.0)	0.51/0.98	

A reduction was observed both in the BDI and JSEQ scores after rTMS for the whole group and in both treatment groups (HLMM: time effect BDI: F2=10.9, p=0.0002, JSEQ: F2=55.2, p<0.0001) with no differences between the groups over time (Table 15).

Table 15. Beck Depression Inventory (BDI) scores (a) and Jenkins Sleep Evaluation Questionnaire (JSEQ) scores (b) in terms of time from the beginning of the rTMS treatment, median, (lower and upper quartiles). Reproduced with the permission of the copyright holders (Sahlsten et al. 2019).

a. BDI

Time	Navigated rTMS group	Non-navigated rTMS group	P value (between-group)	P value (time-effect total group)
Baseline	6.0 (4.0-9.0)	5.5 (3.0-8.0)	0.39	
After	3.0 (0-8.0)	2.0 (1.0-5.5)	0.32 over time	0.0002 over time
3 month	1.5 (0-5.5)	2.0 (1.0-5.5)		

b. JSEQ

Time	Navigated rTMS group	Non-navigated rTMS group	P value (between-group)	P value (time-effect total group)
Baseline	14.0 (9.0-18.5)	13.0 (9.0-15.5)	0.86	
After	4.0 (3.0-5.0)	4.0 (3.5-5.0)	0.48 over time	<0.0001 over time
3 month	12.0 (8.5-15.0)	11.5 (7.0-15.5)		

The rTMS treatment was conducted in the same manner for both groups as considered the patient's perspective; therefore, the patient should not have known which treatment he/she was receiving. After the follow-up, 20/40 patients, however, did guess the protocol correctly.

No major or permanent side effects were observed, but some patients (approximately 2-4 patients/each session) reported local inconvenience due to muscle twitching at the region of the stimulation or mild temporary headaches.

5.4 Study 4

5.4.1 Psychiatric Axis I disorders

The results of the SCID interviews (Axis I and II) are presented in Table 16. Of the 83 patients, 37 (44.6%) had at least one lifetime Axis I disorder. Major depression was the most common lifetime disorder, and it was found in 22 patients (26.5%). Lifetime chronic depression was detected in 6 patients (7.2%); therefore altogether, 28 patients (33.7%) suffered from some lifetime depressive disorder. The severity of tinnitus intensity ($p=0.34$) or annoyance ($p=0.27$) on the VAS scale or the grade of the THI scores ($p=0.30$) had no association with lifetime depressive

disorders. Only 2 patients (2.4%) had current major depression, while 5 patients (6.0%) had current chronic depression, although the lifetime depressive disorder rate was high. Panic disorder represented the second most common lifetime disorder, and it was encountered in 7 patients (8.4%); 6 of them (7.2%) without agoraphobia (AG) and one with AG (1.2%). As stated earlier, active alcohol abuse was an exclusion criterion that affected the results, but only 4 patients (4.8%) had lifetime alcohol dependence. Two patients (2.4%) had lifetime drug abuse; one patient had temporarily used amphetamine, cannabis, and hallucinogens in his youth, and another patient had a current addiction to lorazepam. Table 16 presents the number of patients having any other Axis I disorders, and they ranged from one to five patients. None of the patients suffered from any psychotic disorders.

The SCID I findings in Table 16 are presented, together with the lifetime prevalence rates in the general population of the US National Comorbidity Survey Replication (NCS-R) for a comparison (Kessler et al. 2005a; Kessler et al. 2006). There were no differences between the lifetime prevalence when compared to the general population (Kessler et al. 2005a), apart from a higher rate of lifetime major depressive disorders (26.5% vs. 16.6%) and lower lifetime specific phobia (1.2% vs. 12.5%) as detected in the present tinnitus patients (Table 16). Additionally, the rate of lifetime chronic depression was somewhat higher in our patients (7.2%) than found in the NCS-R survey (2.5%). Further, a comparison between the current prevalence rates (of Study 4) and the 12-month rates for the general population in the NCS-R survey (Kessler et al. 2005b) was conducted. Generally, these rates did not differ, apart from a higher prevalence of current chronic depression (6.0% vs. 1.5%), and a lower prevalence of current specific phobia (1.2% vs. 8.7%) in the patients in Study 4. The prevalence rate of any lifetime Axis I disorder was surprisingly similar in these tinnitus patients (44.6%) as was found in the NCS-R survey (46.4%) (Kessler et al. 2005a). However, the current prevalence rate was somewhat lower in the Study 4 group (18.1%), compared to the 12-month rate (26.2%) in the general population (Kessler et al. 2005b).

Most Axis I disorders emerged before tinnitus in 25 patients (30.1%) compared to 12 patients (14.5%) with the emergence of a psychiatric disorder only after tinnitus. Only 15 patients (18.1%) had a current Axis I disorder. Of the 83 patients, 16 (19.3%) had comorbidity among their lifetime Axis I disorders; 12 patients had 2, 3 patients had 3, and one patient had 5 comorbid Axis I disorders.

5.4.2 Psychiatric Axis II disorders (Personality disorders)

Lifetime personality disorders were detected in 9 patients (10.8%) (Table 16); all had emerged before tinnitus, and 8 (9.6%) were current. One patient had previously (some years ago) been diagnosed with an avoidant and obsessive-compulsive personality in a SCID-II interview, but in the interview for Study 4, the diagnostic criteria for any personality disorder were not met. The lifetime personality disorders discovered were obsessive-compulsive in 7 patients (8.4%), avoidant in 2 (2.4%) and schizoid in one patient (1.2%). Furthermore, 8 patients had at least one cluster C personality disorder, but only one had a cluster A personality disorder (schizoid personality); none of the patients suffered from any cluster B personality disorder. The severity of tinnitus intensity ($p=0.53$) or annoyance ($p=0.43$) on the VAS scale or the grade of their THI scores ($p=0.69$) had no associations with lifetime obsessive-compulsive disorder.

The findings are shown in Table 16 and Figure 19, together with the prevalence rates in the general population for the NCS-R survey for a comparison (Lenzenweger et al. 2007). The similarities between the distributions of personality disorders in tinnitus patients and chronic neuropathic pain patients (Taiminen et al. 2011) are shown in Figure 19. There was no difference between the prevalence rates of Study 4 and the NCS-R survey findings; however, the prevalence rate of cluster C personality disorders was somewhat higher in Study 4, 9.6% vs. 6.0%, especially for the obsessive-compulsive personality disorder at 8.4% vs. 2.4%. The prevalence rate for any personality disorder in Study 4 was very similar to that detected in the general population, i.e., 10.8% vs. 9.1% (Lenzenweger et al. 2007).

Comorbidity among lifetime personality disorders was detected in only one patient (who had both an obsessive-compulsive and an avoidant disorder). Of the 83 patients, 6 had both a lifetime Axis I and an Axis II disorder. Additionally, 6/9 patients (66.7%) who had any lifetime personality disorder also had some comorbid lifetime Axis I disorder.

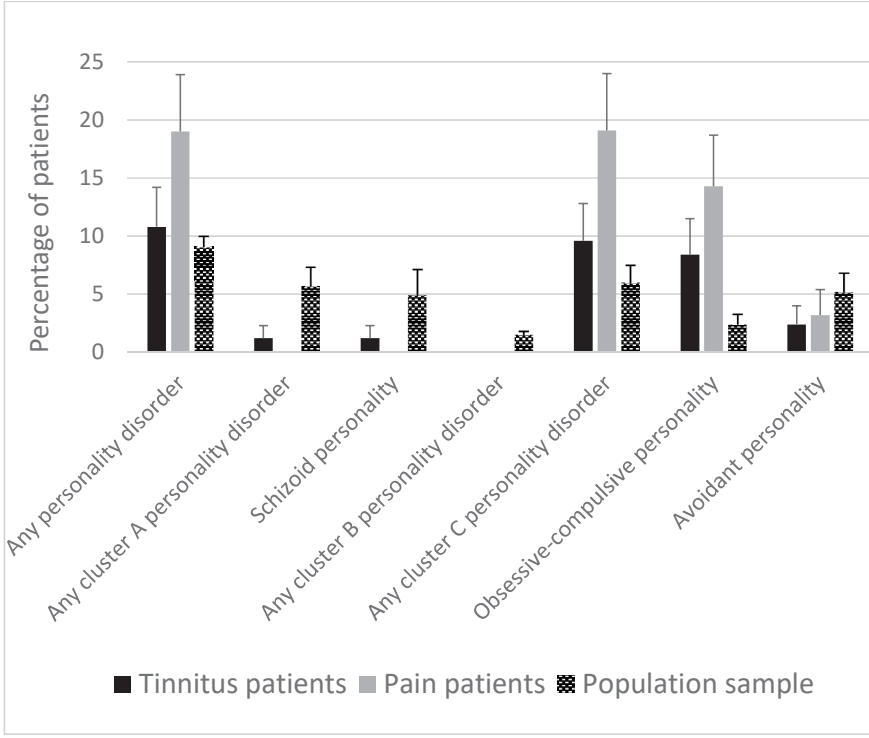

Figure 19. The percentages (+SE) of patients with different personality disorders. The results of Study 4 are presented (Tinnitus patients, n=83) and then compared to chronic facial pain patients, Taiminen et al. (2011) (Pain patients, n=63) and a normal population sample, Lenzenweger et al. (2007) (Population sample, n=214). There were no significant differences between the percentages of tinnitus patients and the population sample. None of the tinnitus or pain patients suffered from any cluster B personality disorders. Reproduced with the permission of the copyright holders (Sahlsten et al. 2018).

Table 16. The prevalence rates of DSM-IV Axis I and II psychiatric disorders in the SCID-I and -II interviews, by onset, in 83 patients with chronic, disturbing tinnitus. To compare the results to the general population, the rates of the National Comorbidity Survey Replication (Kessler et al, 2005 & 2006; Lenzenweger et al, 2007) are also shown. [O]Bipolar disorder and [B]active alcohol dependence were exclusion criteria for TMS treatment; during the study course one patient was discovered to have a bipolar disorder, though. Reproduced with copyright permission (Sahlsten et al. 2018).

Diagnosis	Onset before tinnitus		Onset after tinnitus		Current (previous month)		Lifetime		Lifetime, Kessler et al
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	% (95% CI)
Axis I disorders									
Major depressive disorder	11	13.3 (6.8-22.5)	11	13.3 (6.8-22.5)	2	2.4 (0.3-8.4)	22	26.5 (17.4-37.3)	16.6 (15.8-17.4)
Chronic depression	3	3.6 (0.8-10.2)	3	3.6 (0.8-10.2)	5	6.0 (2.0-13.5)	6	7.2 (1.6-12.8)	2.5 (2.2-2.8)
Bipolar disorder[O]	1	1.2 (0-6.5)	0	0 (0-4.4)	0	0 (0-4.4)	1	1.2 (0-6.5)	3.9 (3.5-4.3)
Generalized anxiety disorder	2	2.4 (0.3-8.4)	2	2.4 (0.3-8.4)	2	2.4 (0.3-8.4)	4	4.8 (1.3-11.9)	5.7 (5.3-6.2)
Specific phobia	1	1.2 (0-6.5)	0	0 (0-4.4)	1	1.2 (0-6.5)	1	1.2 (0-6.5)	12.5 (11.9-13.1)
Social phobia	4	4.8 (1.3-11.9)	1	1.2 (0-6.5)	4	4.8 (1.3-11.9)	5	6.0 (2.0-13.5)	12.1. (11.5-12.7)
Agoraphobia without panic	0	0 (0-4.4)	0	0 (0-4.4)	0	0 (0-4.4)	0	0 (0-4.4)	1.4 (1.2-1.6)
Panic disorder	5	6.0 (2.0-13.5)	2	2.4 (0.3-8.4)	4	4.8 (1.3-11.9)	7	8.4 (3.5-16.6)	4.7 (4.3-5.1)
Panic disorder without agoraphobia	4	4.8 (1.3-11.9)	2	2.4 (0.3-8.4)	3	3.6 (0.8-10.2)	6	7.2 (1.6-12.8)	3.7 (1.7-5.7)
Panic disorder with agoraphobia	1	1.2 (0-6.5)	0	0 (0-4.4)	1	1.2 (0-6.5)	1	1.2 (0-6.5)	1.1 (0-3.1)
Post-traumatic stress disorder	1	1.2 (0-6.5)	0	0 (0-4.4)	0	0 (0-4.4)	1	1.2 (0-6.5)	6.8 (6.3-7.3)
Binge-eating disorder	2	2.4 (0.3-8.4)	0	0	1	1.2 (0-6.5)	2	2.4 (0.3-8.4)	
Alcohol dependence[B]	4	4.8 (1.3-11.9)	0	0 (0-4.4)	0	0 (0-4.4)	4	4.8 (1.3-11.9)	5.4 (4.9-5.9)
Drug dependence	2	2.4 (0.3-8.4)	0	0	1	1.2 (0-6.5)	2	2.4 (0.3-8.4)	3.0 (2.7-3.3)
Any psychotic disorder	0	0 (0-4.4)	0	0 (0-4.4)	0	0 (0-4.4)	0	0 (0-4.4)	
Any axis I disorder	25	30.1 (20.5-41.2)	12	14.5 (7.7-23.9)	15	18.1 (10.5-28.0)	37	44.6 (33.6-55.9)	46.4 (45.1-47.7)
Axis II personality disorders									**Lenzenweger et al**
Any cluster C personality disorder	8	9.6 (4.3-18.1)	0	0 (0-4.4)	7	8.4 (3.5-16.6)	8	9.6 (4.3-18.1)	6.0 (5.4-6.6)
Obsessive-compulsive personality	7	8.4 (3.5-16.6)	0	0 (0-4.4)	6	7.2 (1.6-12.8)	7	8.4 (3.5-16.6)	2.4 (0.8-4.0)
Avoidant personality	2	2.4 (0.3-8.4)	0	0 (0-4.4)	1	1.2 (0-6.5)	2	2.4 (0.3-8.4)	5.2 (2.0-8.3)
Any cluster A personality disorder	1	1.2 (0-6.5)	0	0 (0-4.4)	1	1.2 (0-6.5)	1	1.2 (0-6.5)	5.7 (5.1-6.3)
Schizoid personality	1	1.2 (0-6.5)	0	0 (0-4.4)	1	1.2 (0-6.5)	1	1.2 (0-6.5)	4.9 (0.6-9.2)
Any cluster B personality disorder	0	0 (0-4.4)	0	0 (0-4.4)	0	0 (0-4.4)	0	0 (0-4.4)	1.5 (1.2-1.8)
Any personality disorder	9	10.8 (5.1-19.6)	0	0 (0-4.4)	8	9.6 (4.3-18.1)	9	10.8 (5.1-19.6)	9.1 (8.4-9.9)

5.4.3 Self-rated current psychiatric symptoms

The median BDI score was only 5 (quartiles 2–9, range 0–24), thus belonging to the category of minimal depression; 64 (77.1%) patients scored the minimal, 14 (16.9%) scored mild, 5 (6.0%) scored moderate, and none had severe depression. The median DES score was only 2.4 (quartiles 1.1–4.7, range 0–30) which implies a very low likelihood of a dissociative disorder. Figure 20 (and Table 4 in the Original Article IV) presents the results for different dimensions of the SCL-90, together with the values of a Finnish validation study on the SCL-90, consisting of a Finnish community sample (Holi et al. 1998) for comparison. The mean values for the tinnitus patients were very similar to those of the community sample although the tinnitus patients had a little less interpersonal sensitivity (1.41 vs. 1.74), hostility (1.37 vs. 1.58) and paranoid ideation (1.37 vs. 1.53).

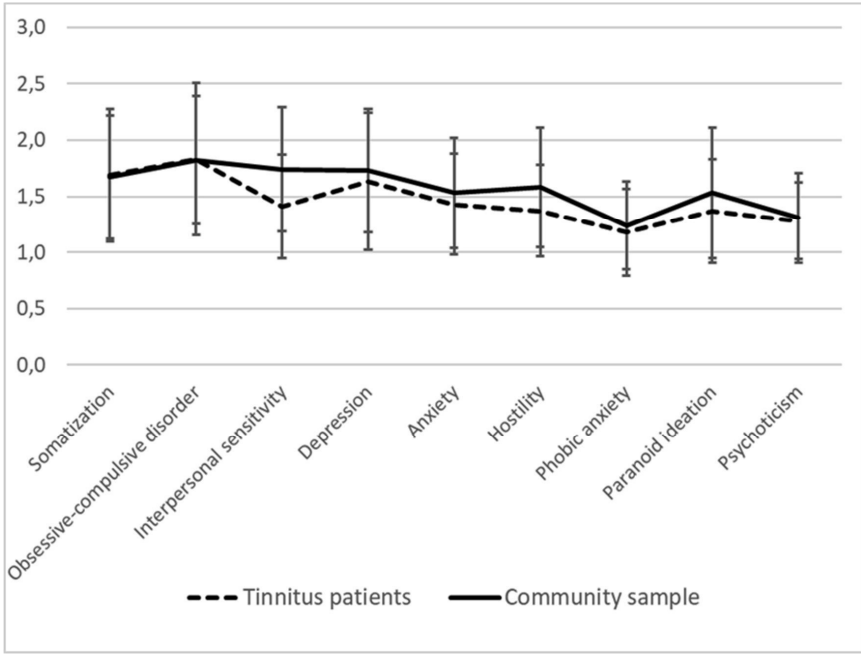

Figure 20. The means (± SD) of the SCL-90 subscales for Study 4 in tinnitus patients and the study of Holi et al (1998), based on a Finnish community sample. To compare the results, +1 was added to the mean results of Holi et al, since in their study the SCL-90 5-point scale of distress went from 0 (not at all) to 4 (extremely) and in the present study from 1 (not at all) to 5 (extremely).

6 DISCUSSION

6.1 Study 1

The results of Study 1 (although only a small open pilot study) implied that it is possible to improve patients' tinnitus symptoms with E-field navigated rTMS. At least a 30% decrease in tinnitus intensity (NRS) occurred in 62% of patients and in annoyance (NRS), by 69%, respectively. Further, tinnitus intensity decreased on average by 39% and annoyance by 45%. The results were somewhat better than in previous studies (Rossi et al. 2007; Mennemeier et al. 2011). However, these effects were temporary, especially with the shorter treatment series. To our knowledge, this was the first study that utilized an E-field, navigated TMS device for tinnitus treatment to achieve a more precise anatomical and tonotopical targeting at the AC than when using "blind" non-navigated rTMS. The results were especially encouraging considering that the patients in Study 1 had very severe, intractable, chronic tinnitus with many complex co-morbidities.

However, Study 1 was a small open pilot study with no randomization or placebo control. Further, the rTMS treatment protocols and patients' features/diagnoses were heterogeneous. Therefore, the promising preliminary results needed a properly controlled comparative study in a larger patient group for confirmation.

6.2 Study 2

Study 2 was a randomized, placebo-controlled study on parallel groups, using E-field rTMS for chronic tinnitus. It showed improvement in the VAS scores (intensity, annoyance, distress) and THI scores, both in the active rTMS group and the placebo group. However, no difference in the therapeutic efficacy existed between the active and placebo treatment groups based on the HLMM model. Therefore, post hoc paired comparisons could not be done although tinnitus intensity was lower in the active group immediately after the treatment and at the 1-month control (Figure 11a, Table 5a). The rate of excellent responders (clinically notable reductions in both all the VAS and THI scores) did not differ between the active and placebo treatment groups, although there were more excellent responders in the active group at the 1-month (42% vs. 15%, p=0.082) and 3-month (37% vs. 10%, p=0.065) controls. At the 6-month control, the THI scores and NRS intensity were still lower when compared to the baseline in both groups.

The absence of significant differences between the active and placebo groups may have partly been due to a wide inter-individual variation in treatment efficacy and a large placebo effect. Generally, the rTMS treatment results are characterized by high interindividual variability (Lehner et al. 2012). In Study 2, there were excellent responders in the active group, with 3 patients' experiencing very little tinnitus or even total silence after the treatment series, whereas 3 other patients did not experience any benefit from the treatment. Further, the placebo rTMS presented a high effect size with Cohen's *d* values up to 0.78. As patient counselling and psychological therapies can have a treatment effect on tinnitus patients (Tunkel et al. 2014), it is possible that some of the high placebo effect was due to the nature of Study 2; the careful clinical assessment, MRIs, and frequent visits to the clinic with caring personnel. It is notable that in an anti-depressant medication trial, up to 40% of the tinnitus patients benefitted from the placebo (Dobie et al. 1993). Additionally, placebo effects are associated with the release of neurotransmitters, such as dopamine and endogenous opioids; also, rTMS exerts its effects at least partially by enhancing the endogenous dopamine-opioid axis (Lefaucheur et al. 2014).

It is notable that during the placebo rTMS treatment, the active E-field varied from 0 to 4 V/m. Therefore, the placebo treatment was not totally inactive, but rather a very weak electrical current that was induced into the brain cortex. As stated before, weak electrical currents, such as those in tDCS, can cause alterations in the polarization of the cortical neurons. In other words, some minor alterations in cortical neuronal activity may have been induced also during the placebo stimulation.

One possible reason for the non-significant difference in treatment efficacy between the active and placebo rTMS rests in the power calculations for Studies 2 and 3. They were based on the results of the pilot study (Study 1), in which the effect size was rather large, perhaps due to high initial symptom severity, which may thus have led to a Type 2 error, i.e., too small groups to show a significant difference between the treatment groups. This assumption is in line with the recent meta-analysis on 720 patients which concluded there was a moderate efficacy of LF rTMS for chronic tinnitus (Soleimani et al. 2016). Nevertheless, based on the results of Study 2, one also needs to consider the possibility of treatment benefits being only placebo effects in both groups. This assumption seems quite unlikely, however, since active rTMS has been shown to significantly influence and modify the brain activity in many functional brain imaging studies (Bestmann et al. 2005; Siebner et al. 2009; Lee et al. 2013; Lamusuo et al. 2017). In addition, the decrease in VAS intensity was more pronounced in the active treatment group immediately and 1 month after the treatment (Figure 11 a), although these post hoc comparisons

are not statistically correct to perform with where there are no significant interaction effects in the HLMM model.

In line with the results of Study 2, other RCTs have also concluded that active rTMS may not be more effective than placebo stimulation for chronic tinnitus (Plewnia et al. 2012; Hoekstra et al. 2013; Piccirillo et al. 2013; Langguth et al. 2014; Landgrebe et al. 2017). All these studies (except for Landgrebe et al. 2017) used some navigation method (although not E-field navigation) and LF stimulation with 100–110% of RMT (except for a continuous theta burst stimulation with 80% of RMT in Plewnia et al. (2012)). Nevertheless, the treatment protocols were different than those in Study 2 which were involving bilateral stimulation (Plewnia et al. 2012; Hoekstra et al. 2013), or a combined stimulation of the temporo-parietal or frontal cortex (Plewnia et al. 2012; Langguth et al. 2014). The number of pulses per session was lower (900–2000 pulses) in 3 studies (Plewnia et al. 2012; Piccirillo et al. 2013; Landgrebe et al. 2017) and was the same as those in Study 2 in 2 studies (Hoekstra et al. 2013; Langguth et al. 2014). The number of treatment sessions varied between 5-20 across all the studies. The median reduction in tinnitus questionnaires after active rTMS treatment varied between 2-10, as it was also in Study 2. There was a slight or significant reduction in tinnitus symptoms in all these studies, but the overall effect of active rTMS, however, was not superior to the placebo.

Contrary to the studies above, several RCTs have observed significant improvement of tinnitus symptoms with rTMS compared to placebo (Khedr et al. 2008; Anders et al. 2010; Marcondes et al. 2010; Mennemeier et al. 2011; Folmer et al. 2015). The mean improvement of the THI scores in the active rTMS group has been somewhat larger than in Study 2 (Khedr et al. 2008; Marcondes et al. 2010). In one study (Anders et al. 2010), THI and Tinnitus Questionnaire scores improved in the active group with no changes in the VAS scores in either group. In Study 2, there was an improvement in all scores (both THI and VAS), but that improvement was not restricted to the active group. In Study 2, 53% of patients in the active group were responders (≥30% decrease) based on the VAS intensity score alone. This result is somewhat better than in one previous study that presented a positive efficacy based on a 43% responder rate (≥ 33% reduction in tinnitus loudness) and a significant VAS reduction, but only after active, not after placebo treatment (Mennemeier et al. 2011). In another study, there was a 56% responder rate in the active rTMS group based on the Tinnitus Functional Index scores after the serial rTMS (Folmer et al. 2015). This result is in line with the responder rate of 58% in Study 2 here, based on the reduction of the THI scores alone. Thus, the primary outcome measures may greatly influence the final conclusions for the rTMS studies on tinnitus.

6.3 Study 3

In Study 3, chronic tinnitus improved significantly in both the rTMS study groups, but nrTMS was not superior over non-navigated rTMS. In fact, the treatment effect was even better in the non-navigated group, but only for tinnitus intensity for both the VAS and NRS scores. Also, Cohen's *d* values showed a similar trend in favor of non-navigated rTMS.

The main results were in line with another study on tinnitus that compared nrTMS (based on the brain MRI) with non-navigated rTMS (based on the 10-20 EEG system) (Noh et al. 2017b). They reported a significant reduction of THI and VAS scores in both groups with no differences between the groups, i.e., results similar to Study 3 here. They presented somewhat better responder rates, 92% in the navigated group and 89% in the non-navigated group based on a reduction of THI scores of at least by 7, compared to our rates of 75% and 80% (THI score decrease by ≥6), respectively. The number of patients, the stimulation site, and the protocol differed since they treated only 22 patients stimulating both the left AC and the left prefrontal cortex with a 2000+1000 pulses/session and for only 4 days. Despite these differences, the results were surprisingly similar, probably one reason being the lack of a placebo group in both studies.

Langguth et al. (2014) compared PET-guided nrTMS and sham over the left AC, non-navigated (based on the 10-20 EEG system) rTMS over the left temporal cortex, and the non-navigated rTMS combined over the left frontal and the temporal cortices. There was a significant tinnitus improvement for all 3 active conditions, but as in Study 3, no significant differences between the treatment groups existed, although there was a trend indicating that the combined frontal and temporal rTMS could be the most efficient protocol (Langguth et al. 2014). In another study using a sham-controlled crossover design, 16 patients received active rTMS over the left AC: 8 patients received nrTMS (based on the stereotaxic navigation) and 8 patients, non-navigated rTMS (Rossi et al. 2007). There was a significant transient improvement of tinnitus after active rTMS, compared to the sham; nevertheless, the results of the active rTMS procedures were not systemically compared.

In Study 3, the effect size of Cohen's *d* for tinnitus intensity after nrTMS indicated a modest treatment response, and after the non-navigated rTMS, a good/excellent response. It may be that the target localization for the non-navigated rTMS was more optimal for tinnitus treatment. Notably, non-navigated methods have been inaccurate (by 1-2 cm) for the anatomical targets actually being stimulated (Langguth et al. 2006; Ahdab et al. 2010). Recently it was demonstrated that the stimulation spot used according to the 10-20 EEG system (Langguth et al. 2006)

is on average 10.4 mm superior and 10.8 mm posterior to the scalp location that minimizes the distance to the primary AC, i.e., the optimal cortical target to reach the AC (Theodoroff et al. 2018). Further, in the non-navigated rTMS (in Study 3), the measured coil target was not as precise as in nrTMS, and the stability of the coil was monitored only visually; therefore, the variability during/between the sessions must have been larger than when using nrTMS. Therefore, non-navigated rTMS may have stimulated a wider brain area than nrTMS, including perhaps a more optimal spot (more posterior/cranial – probably nearer to the temporoparietal association areas, Figure 2) for tinnitus control.

Nevertheless, based on Study 3 and the previous literature, it appears that the coil localization method is not a critical factor in the treatment effect of rTMS for tinnitus (Langguth et al. 2014; Noh et al. 2017b). First, the optimal target for rTMS stimulation in tinnitus is still unclear (Langguth et al. 2010). The most frequently used target is the left temporoparietal cortex that is overlying the more deeply situated AC. The rTMS coil is typically applied over the Sylvian fissure or the STG. The primary AC is buried deep within this region, so the magnetic field more likely spreads to the more superficial secondary auditory areas rather than directly influencing the primary AC (Langguth et al. 2010). Therefore, the tinnitus suppressing effect is explained by an activation of the functional neural connections existing between the secondary and the primary AC (De Ridder et al. 2006). Probably the optimal rTMS target is localized in the more superficial secondary AC so to enable an indirect stimulation of the primary AC (Langguth et al. 2010). Interestingly, in the experimental studies on rTMS for pain, the rTMS influence may be larger in the nearby adjacent region than directly on the "hot spot" of the stimulation (Hoogendam et al. 2010; Lefaucheur et al. 2014).

In Study 3, the coil was placed to induce downward (caudal) electric currents in the brain for technical reasons, whereas in Studies 1 and 2, the induced currents were in an upward direction. The effects of posterior-anterior (PA) and anterior-posterior (AP) currents on the motor cortex may be mediated by different neuronal circuits (Ni et al. 2011; Hannah & Rothwell 2017). In addition, PA current direction is considered more effective than AP for inducing MEPs (Andre-Obadia et al. 2008; Davila Pérez et al. 2018). There is, however, a need for more research on the current/field directions for rTMS efficacy in tinnitus, as many studies on rTMS have not stated the direction of the main induced electric field current. Besides stimulating the AC, multiple target stimulation, including the DLPFC, may enhance efficacy (Lehner et al. 2013; Lehner et al. 2016). On the other hand, although non-auditory brain structures participate in tinnitus pathophysiology, rTMS on non-auditory cortical sites alone seems to be unable to suppress tinnitus (Noh et al. 2017a).

Secondly, the cortical area stimulated by rTMS is approximately 2x2 cm large, and inter-individual differences in skull-brain relations differ at around the same range (Langguth et al. 2006; Langguth et al. 2010). Therefore, the precision of neuronavigation may not be necessary if the correct target is no more than 1 cm away from the hotspot of the coil. Hence, the primary AC may have been within the rTMS stimulation coverage region in both treatment groups, although possibly in some patients through the initial activation of the secondary associative cortices.

6.4 Factors influencing and predicting rTMS effects

Different factors may produce opposing results in parallel RCTs on rTMS for chronic tinnitus (Lefaucheur et al. 2014; Londero et al. 2017). The rTMS system, navigation method, treatment targets, stimulation protocols and patient groups differed considerably between the studies. In a large meta-analysis of rTMS treatment for depression, the results were better in rTMS studies with fewer stimuli per session (Kedzior et al. 2014). In Study 1 (showing better treatment effects, although without a placebo group), mostly 1800–2000 pulses/session of rTMS were used, compared to the 4000 pulses used in Studies 2 and 3. Stimulating the brain with too many stimuli at one time may lead to neural network saturation and consequently, to a cancellation and a decrease in the therapeutic effect of rTMS (Kedzior et al. 2014). Furthermore, it is known that for rTMS in depression, the results may be better after a longer serial treatment (>2 weeks); therefore, the two-week protocol of Studies 2 and 3 may have been too short to produce long lasting effects.

Tinnitus severity has been proposed to be a positive predictor of rTMS effect (Lehner et al. 2012) and may have affected the results of Studies 2 and 3, as these patients presented rather mild symptomatology (whereas the patients in Study 1 had more severe tinnitus). Further, it has been proposed that a longer duration of tinnitus (De Ridder et al. 2005) and hearing deficit (Kleinjung et al. 2007) may decrease the efficacy of rTMS treatment. However, in Studies 1-3, the duration of tinnitus or hearing deficit was not associated with the treatment efficacy. Additionally, it has been suggested that a patient's old age may reduce the efficacy of rTMS treatment (Langguth et al. 2008). In Studies 1 and 3, age was not found to be associated with the treatment results. However, in Study 2 (considering tinnitus intensity) in both the active and placebo groups, surprisingly, older patients (>60 years) benefitted more from the treatment than did the younger patients ($p=0.0013$). Overall, the patient groups of Studies 1-3 should have been larger to better evaluate the demographic and clinical predictors for the rTMS treatment outcome. Generally, the results of rTMS for tinnitus do differ vastly

across the studies, thus supporting the statement that there are no established and reliable demographic or clinical predictors for the ideal treatment outcome (Lehner et al. 2012).

As stated earlier, the rTMS treatment results are characterized by high inter-individual variability (Langguth et al. 2008; Lehner et al. 2012). One reason for this aspect is the genetic constitution of the individuals, as it has, e.g., been suggested that the val/met polymorphism of the brain derived neurotrophic factor (BDNF) gene may cause individual differences in the effect of rTMS by altering the tendency for synaptic plasticity (rTMS being effective in the val/val genotype) (Cheeran et al. 2008; Hoogendam et al. 2010). Another proposed genetic factor is the dopamine D2 receptor C957T polymorphism, which seems to determine thermal sensitivity and analgesic rTMS effects (T/T genotype is more likely to show analgesic changes in thermal threshold measurements after rTMS) (Jääskeläinen et al. 2014). These genetic polymorphisms were analyzed for the patients in Studies 2 and 3, but their effects on rTMS treatment results will be presented in future publications.

6.5 Common and distinctive aspects of Studies 1-3

In Studies 1-3, some discrepancies between a subjective appraisal of benefit and the NRS/VAS/THI scores were observed. For example, 2 patients reported GIC 0, despite a slight decrease of tinnitus intensity and annoyance (20%) in one of them (Study 1). However, in Study 2 in the active group, the rate of excellent responders (26%) was in line with the rate of positive GIC values that were measured immediately after rTMS series. Furthermore, despite significant reductions in VAS and THI scores in Studies 2 and 3, mostly no changes were observed in the psycho-acoustically measured loudness or pitch of tinnitus in Study 2, except for the improvement in loudness of the tinnitus in the left ear for the whole group in Study 3. Overall, the results of psycho-acoustic testing of tinnitus perception have been demonstrated to have little if any correlation with the degree of tinnitus impact (Henry et al. 2005). In conclusion, there is a need for a multimodal assessment of rTMS efficacy, as different outcome measures will elucidate distinct aspects of the possible therapeutic effects.

In Study 1, 77% of patients felt a subjective benefit from the treatment, based on positive GIC values alone. Study 1 was a small, open pilot study, and thus, the results were not directly comparable with Studies 2 and 3. Study 2 was the only study with a placebo group, as in Study 3 all patients received active rTMS. However, the results of Studies 2 and 3 had the same tendencies and are quite similar, although the patients in Study 3 showed somewhat better responses

throughout the follow-up time. In Study 2, 26% of the patients in the active group reported positive GIC, and in Study 3, 28% of the patients did so, respectively. The rate of excellent responders immediately after rTMS was 26% in the active group (Study 2) and 38% in the entire study group (Study 3), respectively. The rate of excellent responders was even better at the 1-month control, being 42% in the active group (placebo group only 15%, p=0.0082) (Study 2) and 40% in Study 3. The decrease in VAS and THI scores persisted for the entire follow-up time in both Studies 2 and 3. The effect size in Cohen's *d* for tinnitus intensity calculated between the baseline and post-treatment time points fluctuated somewhat between Studies 2 and 3, yet, the values were quite similar between the active group in Study 2 (0.92-0.82) and the non-navigated group in Study 3 (1.07-0.55). One could consider that the similarities in the treatment outcomes of the active rTMS for Studies 2 and 3 may demonstrate a true treatment effect of rTMS instead of just a placebo effect.

In Studies 2 and 3, there was a small improvement in the BDI scores after treatment for the whole group and in both treatment groups separately, but no significant differences between the groups over time. So theoretically, reductions in the THI scores could have been due to the treatment effects of depression rather than any modulation of the tinnitus network itself. This seems unlikely though, since only the left AC was stimulated in both studies with no multi-site stimulation, such as stimulation of the dorsolateral prefrontal cortex, the main target of rTMS for depression control (Lefaucheur et al. 2014). In addition, these patients were not depressed at the baseline (median BDI scores only 4.0-6.0). Therefore, although there was a small improvement in the BDI scores for the whole group, that change was not clinically meaningful, given the low BDI scores noted at the baseline.

In Studies 1-3, rTMS proved to be feasible, safe, and well tolerated for chronic tinnitus. Both rTMS devices were easy and practical to use. There were no major side effects, such as seizures, but some patients did report local irritation due to muscle twitching at the stimulation side (for them the stimulus intensity was lowered) and mild temporary side-effects, like headaches. Only 3 patients in the total study population of Studies 1-3 discontinued the intervention. One patient discontinued the treatment after 8 sessions because her migraine got worse (Study 1) and 2 patients felt the stimulation to be uncomfortable and had difficulty arranging time for the study (Study 2).

In conclusion, the most efficient protocol, location, coil orientation, and side for rTMS stimulation in tinnitus still needs further rigorous controlled studies. Individual fMRI or PET imaging of the most hyperactive region of the cortex, however, could be useful when choosing the most optimal treatment target (Plewnia et al. 2007). The role of multiple cortical target stimulation (Lehner et al.

2013) and the optimal protocol for rTMS maintenance therapy also needs more clarification. One solution for these issues could be redirecting the rTMS treatment into a more individualized form (Kreuzer et al. 2017). In the future, RCTs with proper patient selection and characterization, significantly larger patient groups, and standardized treatment protocols are still needed to determine the value of (neuronavigated) rTMS for tinnitus.

6.6 Study 4

The main findings of Study 4 were the rather high prevalence rates of lifetime major depression (MD) and obsessive-compulsive personality disorder (O-CPD) in chronic tinnitus patients. Low rates of specific phobia and current MD were detected, although there was an elevated rate of current chronic depression. Most of the Axis I disorders had occurred before the onset of tinnitus. In addition, no cluster B personality disorders (PD) or psychotic disorders were found, and the patients had a very low likelihood of any dissociative disorder.

In Study 4, the rate of lifetime MD at 26.5%, was larger than that reported for the general population of the NCS-R survey at 16.6% (Kessler et al. 2005a). This result is notable, especially considering that 59% of the patients in Study 4 were men, and generally, women tend to be more vulnerable to mood disorders, such as depression, in general population studies (Kessler et al. 2005a). Nevertheless, the rate of current (previous month) MD was somewhat lower than the corresponding 12-month rate in the NCS-R survey of 6.7% (Kessler et al. 2005b). Hence, although tinnitus patients are vulnerable to episodes of MD, they seem to recover well, as the current rate was low. Further, the rate of current chronic depression at 6.0% was higher than the 12-month rate seen in the NCS-R survey at 1.5% (Kessler et al. 2005b). Yet, the lifetime rates did not differ significantly (although they were somewhat higher in Study 4). The prevalence rates of major and chronic depression were the same before and after the occurrence of tinnitus, which implies that tinnitus does not predispose patients to depression. The relatively large lifetime rate of depressive disorders (33.7%) in Study 4 was in line with a study using SCID to analyze tinnitus patients (Malakouti et al. 2011), and yet, even rates up to 77.5% (Sullivan et al. 1988) have been published (Table 1).

In Study 4, no differences existed between the lifetime prevalence rates of anxiety disorders as compared to the general population, except for the very low rate of specific phobia seen in Study 4. Only one patient had a lifetime specific phobia (against snakes) compared to the significantly larger general population prevalence of 12.5% (Kessler et al. 2005a). This finding could be coincidental and partially based on the male dominance in our study, as women are more vulnerable to

anxiety disorders, such as phobias (Kessler et al. 2005a). In Study 4, both the lifetime prevalence rate of anxiety disorders at 21.7% and the current rate, 13.3%, were evidently lower than those detected in other studies that used validated diagnostic interviews on tinnitus patients and reported lifetime prevalence at around 45% (Holgers et al. 2005; Malakouti et al. 2011; Zöger et al. 2001) (Table 1), and a 28–49% current rate (Belli et al. 2008; Zöger et al. 2006). The tinnitus patients in Study 4 expressed rather mild symptomatology (median THI score 32), which may partially explain the lower rate of anxiety disorders in our material.

An important finding of Study 4 is that tinnitus did not seem to predispose patients to Axis I psychiatric disorders, since most of those disorders occurred before tinnitus (in 25 patients, compared to 12 for whom the onset occurred after tinnitus). Furthermore, only 15 patients had a current Axis I disorder. None of the patients suffered from psychotic disorders, so there was no connection made between tinnitus and psychotic disorders.

In Study 4, 10.8% of the patients suffered from at least one PD. This rate is about the same as that reported in the NCS-R general population survey (Lenzenweger et al. 2007), but larger than the prevalence rate of only 3% in one study that evaluated tinnitus patients using SCID (Belli et al. 2008), and yet, markedly lower than the 50% rate in another study (Erlandsson & Persson 2006) (Table 1). Belli et al. (2008), investigated 90 patients with ‘‘annoying tinnitus’’, although symptom severity was not evaluated using any numerical measures. Further, they excluded all patients with significant medical and/or psychiatric pathologies, such as schizophrenia and dementia. Erlandsson and Persson (2006) evaluated a sub-group of only 18 tinnitus patients with depressed mood (having an average BDI score of 19.9), which may explain the differences when compared to our larger group of patients. The rate of PDs in Study 4 was also lower than a previous 19% rate that was based only on a self-report questionnaire (Marciano et al. 2003).

In Study 4, most PDs belonged to the cluster C, and only one patient had a cluster A disorder. The rate of O-CPD at 8.4%, was somewhat larger than that in the NCS-R survey and Belli et al. (2008), but notably lower than that in Erlandsson and Persson (2006). Zöger et al (2001) published a 49% prevalence rate of cluster C personality traits in tinnitus patients; nevertheless, personality traits should not be directly compared to a psychiatric diagnosis of PD. Uncontrollable tinnitus can produce intractable distress for patients with O-CPD, as these patients exhibit an extensive pattern of preoccupation with perfectionism and mental control, even at the cost of efficiency and flexibility (American Psychiatric Association 1994). Hence, patients with O-CPD may also be more prone to seek help for their tinnitus and fixate on the symptoms. No patient in Study 4 suffered from a cluster B PD, although the NCS-R survey reported a 1.5% prevalence rate (Lenzenweger et al.

2007). One reason may have been the rather high age of our patients (median 56.0 years), as cluster B PDs usually decrease with advancing age (Reich et al. 1988).

Based on the self-rated, current psychiatric symptoms alone, our tinnitus patients were psychologically quite healthy and resilient. The median BDI was low (5.0), the mean values of the SCL-90 were almost identical to those in a Finnish community sample (Figure 20) (Holi et al. 1998), and the median DES score was only 2.4 (lower than the median of 4.38 reported for adults in a DES study) (Bernstein & Putnam 1986). Hence, this result implies that tinnitus patients are resilient to dissociative experiences, and tinnitus seems not to be associated with dissociative auditory hallucinations.

Generally, tinnitus patients appeared to be psychologically somewhat more resilient than pain patients; however, the profile of psychiatric and personality disorders occurring in these two conditions seem notably similar (Figure 19). In a study of 63 patients with chronic neuropathic pain evaluated using SCID (Taiminen et al. 2011), an increased rate of lifetime MD (30.2%) and current MD (12.7%) were observed. Additionally, the rate of any PD was elevated (19.0%) in chronic pain patients, but due only to a growth in cluster C disorders as was the case also in most of the present tinnitus patients. The prevalence rates in pain patients were somewhat higher than those in Study 4, especially the rate of O-CPD (14.3%); however, the profiles of Axis I and Axis II disorders, as well as disorders with increased rates compared to the population samples, appeared to be quite similar.

6.7 Study 4 and rTMS

In Study 4, the patients presented with elevated rates of MD and O-CPD. However, they had recovered well from previous depressive episodes, which indicated good neuronal plasticity and resilience (Castren 2013). MD has been associated with reduced brain dopamine levels (Lambert et al. 2000), and O-CPD with dysfunctional brain dopamine activity (Olver et al. 2009). Generally, cluster C personality disorders are characterized by low novelty seeking and fearfulness, and these features have been associated with low brain dopamine activity (Zald et al. 2008). Further, dopamine is supposed to regulate auditory processing and gating also (Du & Jansen 2011). Dopaminergic receptors are located both in the cochlea and in the central nervous system network, and any dysfunction in these dopaminergic pathways has been proposed as participating in the pathogenesis of tinnitus (Langguth et al. 2011; Rauschecker et al. 2015) as it does in chronic pain (Hagelberg et al. 2004; Jääskeläinen et al. 2014; Martikainen et al. 2018). The psychiatric Axis I and Axis II disorders in Study 4 are mostly associated with brain

dopamine hypo- or dysfunction, thus supporting the importance of frontostriatal dopamine circuits in chronic tinnitus and chronic neuropathic pain. Low dopamine tone with deficient top-down inhibitory control may serve as a common predisposing factor for these chronic conditions and the psychiatric comorbidity associated with them.

The patients of Study 4 participated in Studies 2 and 3 that evaluated rTMS for chronic tinnitus. It is notable that rTMS exerts its effects by altering neuronal plasticity by releasing dopamine and endogenic opioids (Lamusuo et al. 2017), and it has also been successfully used to treat depression and neuropathic pain (Lefaucheur et al. 2014). However, more research is needed to establish the therapeutic efficacy of rTMS for tinnitus control. As stated earlier, there are similarities in the pathophysiology of depression, neuropathic pain and tinnitus. If rTMS is used in the future to treat tinnitus, it will be useful to screen for depression (for example with the BDI), as it is possible to treat comorbid depression (and even neuropathic pain) during the same rTMS session using the same device.

7 CONCLUSIONS

The following conclusions can be drawn from this thesis:

1. RTMS is feasible, safe, and well tolerated for the treatment of chronic tinnitus. Both rTMS devices utilized in this study were easy and practical to use.

2. Despite significant improvements in tinnitus measures during the study period, active E-field navigated rTMS to the left auditory cortex was no more effective than the placebo stimulation. A large placebo effect and a rather small study group in combination with a wide inter-individual variation in the efficacy may explain these results. Cohen's *d* for tinnitus intensity was up to 0.92 in the active rTMS group and 0.78 in the placebo group. The rate of excellent responders to active rTMS treatment was up to 42%, and 15% in placebo treatment.

3. Both neuronavigated and non-navigated rTMS were effective for chronic tinnitus; however, the method of coil localization was not a critical factor for treatment outcome. One reason is that the exact optimal target for rTMS stimulation in tinnitus is still uncertain.

4. Tinnitus patients are prone to episodes of major depression, and they often have obsessive-compulsive and other type C personality features, similar to chronic pain patients. Psychiatric disorders seem to be comorbid or predisposing conditions rather than consequences of tinnitus. None of the patients suffered from psychotic disorders. Overall, tinnitus patients are psychologically quite resilient, and therefore, suitable for receiving novel treatment options, such as therapeutic brain stimulation

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Psalm 8: 1, 3-4

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REFERENCES

Adamchic, I., Langguth, B., Hauptmann, C., & Tass, P. A. (2012). Psychometric evaluation of visual analog scale for the assessment of chronic tinnitus. *American Journal of Audiology, 21*(2), 215-225. doi:10.1044/1059-0889(2012/12-0010)

Ahdab, R., Ayache, S. S., Brugieres, P., Goujon, C., & Lefaucheur, J. (2010). Comparison of "standard" and "navigated" procedures of TMS coil positioning over motor, premotor and prefrontal targets in patients with chronic pain and depression. *Neurophysiologie Clinique-Clinical Neurophysiology, 40*(1), 27-36. doi:10.1016/j.neucli.2010.01.001

Allen, E. A., Pasley, B. N., Duong, T., & Freeman, R. D. (2007). Transcranial magnetic stimulation elicits coupled neural and hemodynamic consequences. *Science, 317*(5846), 1918-1921. doi:10.1126/science.1146426

American Psychiatric Association (Ed.). (1994). *Diagnostic and statistical manual of mental disorders (DSM-IV). 4th ed.* Washington, DC: APA.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5. ed. ed.). Washington, DC [u.a.]: American Psychiatric Publ.

Anders, M., Dvorakova, J., Rathova, L., Havrankova, P., Pelcova, P., Vaneckova, M., Jech, R., Holcat, M., Seidl, Z., & Raboch, J. (2010). Efficacy of repetitive transcranial magnetic stimulation for the treatment of refractory chronic tinnitus: A randomized, placebo controlled study. *Neuroendocrinology Letters, 31*(2), 238-249.

Andre-Obadia, N., Mertens, P., Gueguen, A., Peyron, R., & Garcia-Larrea, L. (2008). Pain relief by rTMS: Differential effect of current flow but no specific action on pain subtypes. *Neurology, 71*(11), 833-840. doi:10.1212/01.wnl.0000325481.61471.f0

Araujo, M., Oliveira, C. A., & Bahmad, F. M. (2005). Intratympanic dexamethasone injections as a treatment for severe, disabling tinnitus - does it work? *Archives of Otolaryngology-Head & Neck Surgery, 131*(2), 113-117. doi:10.1001/archotol.131.2.113

Arda, H. N., Tuncel, U., Akdogan, O., & Ozluoglu, L. N. (2003). The role of zinc in the treatment of tinnitus. *Otology & Neurotology, 24*(1), 86-89. doi:10.1097/00129492-200301000-00018

Ayache, S. S., Ahdab, R., Chalah, M. A., Farhat, W. H., Mylius, V., Goujon, C., Sorel, M., & Lefaucheur, J. (2016). Analgesic effects of navigated motor cortex rTMS in patients with chronic neuropathic pain. *European Journal of Pain, 20*(9), 1413-1422. doi:10.1002/ejp.864

Baguley, D. M., Jones, S., Wilkins, I., Axon, P. R., & Moffat, D. A. (2005). The inhibitory effect of intravenous lidocaine infusion on tinnitus after translabyrinthine removal of vestibular schwannoma: A double-blind, placebo-controlled, crossover study (vol 26, pg 169, 2005). *Otology & Neurotology, 26*(6), 1264.

Baguley, D., & Atlas, M. (2007). Cochlear implants and tinnitus. *Prog Brain Res, 166*, 347-355. doi:10.1016/S0079-6123(07)66033-6

Baguley, D., McFerran, D., & Hall, D. (2013). Tinnitus. *Lancet, 382*(9904), 1600-1607. doi:10.1016/S0140-6736(13)60142-7

Bahmad, F., Venosa, A., & Oliveira, C. (2006). Benzodiazepines and GABAergics in treating severe disabling tinnitus of predominantly cochlear origin. *The International Tinnitus Journal, 12*(2), 140-144.

Baldo, P., Doree, C., Molin, P., McFerran, D., & Cecco, S. (2012). Antidepressants for patients with tinnitus. *The Cochrane Database of Systematic Reviews, 9*, CD003853. doi:10.1002/14651858.CD003853.pub3 [doi]

Barker, A. T. (1999). In Paulus, W Hallett, M Rossini, PM Rothwell,JC (Ed.), *The history and basic principles of magnetic nerve stimulation*. AMSTERDAM; SARA BURGERHARTSTRAAT 25, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS: ELSEVIER SCIENCE BV.

Barker, A. T., & Jalinous, R. (1985). Non-invasive magnetic stimulation of human motor cortex. *Lancet, 1*(8437), 1106-1107.

Barr, M. S., Farzan, F., Arenovich, T., Chen, R., Fitzgerald, P. B., & Daskalakis, Z. J. (2011). The effect of repetitive transcranial magnetic stimulation on gamma oscillatory activity in schizophrenia. *Plos One, 6*(7), e22627. doi:10.1371/journal.pone.0022627

Bartels, H., Staal, M. J., Holm, A. F., Mooij, J. J. A., & Albers, F. W. J. (2007). Long-term evaluation of treatment of chronic, therapeutically refractory tinnitus by neurostimulation. *Stereotactic and Functional Neurosurgery, 85*(4), 150-157. doi:10.1159/000099073

Belli, S., Belli, H., Bahcebasi, T., Ozcetin, A., Alpay, E., & Ertem, U. (2008). Assessment of psychopathological aspects and psychiatric comorbidities in patients affected by tinnitus. *European Archives of Oto-Rhino-Laryngology, 265*(3), 279-285. doi:10.1007/s00405-007-0440-8

Ben-Menachem, E. (2001). Vagus nerve stimulation, side effects, and long-term safety. *Journal of Clinical Neurophysiology, 18*(5), 415-418. doi:10.1097/00004691-200109000-00005

Bennett, M. H., Kertesz, T., Perleth, M., Yeung, P., & Lehm, J. P. (2012). Hyperbaric oxygen for idiopathic sudden sensorineural hearing loss and tinnitus. *Cochrane Database of Systematic Reviews,* (10), CD004739. doi:10.1002/14651858.CD004739.pub4

Bernstein, E. M., & Putnam, F. W. (1986). Development, reliability, and validity of a dissociation scale. *Journal of Nervous and Mental Disease, 174*(12), 727-735. doi:10.1097/00005053-198612000-00004

Bestmann, S., Baudewig, J., Siebner, H. R., Rothwell, J. C., & Frahm, J. (2005). BOLD MRI responses to repetitive TMS over human dorsal premotor cortex. *NeuroImage, 28*(1), 22-29. doi:10.1016/j.neuroimage.2005.05.027

Bindman, L. J., Lippold, O., & Redfearn, J. W. (1962). Long-lasting changes in level of electrical activity of cerebral cortex produced by polarizing currents. *Nature, 196*(4854), &. doi:10.1038/196584a0

Blasco, M. A., & Redleaf, M. I. (2014). Cochlear implantation in unilateral sudden deafness improves tinnitus and speech comprehension: Meta-analysis and systematic review. *Otology & Neurotology, 35*(8), 1426-1432.

Blood, A. J., Zatorre, R. J., Bermudez, P., & Evans, A. C. (1999). Emotional responses to pleasant and unpleasant music correlate with activity in paralimbic brain regions. *Nature Neuroscience, 2*(4), 382-387. doi:10.1038/7299

Brown, P. (2006). Bad oscillations in parkinson's disease. *Journal of Neural Transmission-Supplement,* (70), 27-30.

Brown, P., & Molliver, M. E. (2000). Dual serotonin (5-HT) projections to the nucleus accumbens core and shell: Relation of the 5-HT transporter to amphetamine-induced neurotoxicity. *Journal of Neuroscience, 20*(5), 1952-1963.

Burger, J., Frank, E., Kreuzer, P., Kleinjung, T., Vielsmeier, V., Landgrebe, M., Hajak, G., & Langguth, B. (2011). Transcranial magnetic stimulation for the treatment of tinnitus: 4-year follow-up in treatment responders--a retrospective analysis. *Brain Stimulation, 4*(4), 222-227. doi:10.1016/j.brs.2010.11.003 [doi]

Busto, U., Sellers, E. M., Naranjo, C. A., Cappell, H., Sanchezcraig, M., & Sykora, K. (1986). Withdrawal reaction after long-term therapeutic use of benzodiazepines. *New England Journal of Medicine, 315*(14), 854-859. doi:10.1056/NEJM198610023151403

Cacace, A., Hu, J., Romero, S., Xuan, Y., Burkard, R., & Tyler, R. (2017). Glutamate is down-regulated and tinnitus loudness-levels decreased following rTMS over auditory cortex of the left hemisphere: A prospective randomized single-blinded sham-controlled cross-over study. *Hearing Research,* doi:10.1016/j.heares.2017.10.017

Calabresi, P., Picconi, B., Tozzi, A., & Di Filippo, M. (2007). Dopamine-mediated regulation of corticostriatal synaptic plasticity. *Trends in Neurosciences, 30*(5), 211-219. doi:10.1016/j.tins.2007.03.001

Canali, P., Sarasso, S., Rosanova, M., Casarotto, S., Sferrazza-Papa, G., Gosseries, O., Fecchio, M., Massimini, M., Mariotti, M., Cavallaro, R., Smeraldi, E., Colombo, C., & Benedetti, F. (2015).

Shared reduction of oscillatory natural frequencies in bipolar disorder, major depressive disorder and schizophrenia. *Journal of Affective Disorders, 184*, 111-115. doi:10.1016/j.jad.2015.05.043

Castren, E. (2013). Neuronal network plasticity and recovery from depression. *Jama Psychiatry, 70*(9), 983-989. doi:10.1001/jamapsychiatry.2013.1

Cheeran, B., Talelli, P., Mori, F., Koch, G., Suppa, A., Edwards, M., Houlden, H., Bhatia, K., Greenwood, R., & Rothwell, J. C. (2008). A common polymorphism in the brain-derived neurotrophic factor gene (BDNF) modulates human cortical plasticity and the response to rTMS. *Journal of Physiology-London, 586*(23), 5717-5725. doi:10.1113/jphysiol.2008.159905

Cheung, S. W., & Larson, P. S. (2010). Tinnitus modulation by deep brain stimulation in locus of caudate neurons (area lc). *Neuroscience, 169*(4), 1768-1778. doi:10.1016/j.neuroscience.2010.06.007

Choi, S. J., Lee, J. B., Lim, H. J., In, S. M., Kim, J., Bae, K. H., & Choung, Y. (2013). Intratympanic dexamethasone injection for refractory tinnitus: Prospective placebo-controlled study. *Laryngoscope, 123*(11), 2817-2822. doi:10.1002/lary.24126

Coelho, C. B., Tyler, R., & Hansen, M. (2007). Zinc as a possible treatment for tinnitus. *Tinnitus: Pathophysiology and Treatment, 166*, 279-285. doi:10.1016/S0079-6123(07)66026-9

Coelho, C., Witt, S. A., Ji, H., Hansen, M. R., Gantz, B., & Tyler, R. (2013). Zinc to treat tinnitus in the elderly: A randomized placebo controlled crossover trial. *Otology & Neurotology, 34*(6), 1146-1154.

Coles, R., Thompson, A. C., & Odonoghue, G. M. (1992). Intratympanic injections in the treatment of tinnitus. *Clinical Otolaryngology, 17*(3), 240-242. doi:10.1111/j.1365-2273.1992.tb01835.x

Crane, R. A., Camilon, M., Nguyen, S., & Meyer, T. A. (2015). Steroids for treatment of sudden sensorineural hearing loss: A meta-analysis of randomized controlled trials. *Laryngoscope, 125*(1), 209-217. doi:10.1002/lary.24834

Cristancho, P., Cristancho, M. A., Baltuch, G. H., Thase, M. E., & O'Reardon, J. P. (2011). Effectiveness and safety of vagus nerve stimulation for severe treatment-resistant major depression in clinical practice after FDA approval: Outcomes at 1 year. *Journal of Clinical Psychiatry, 72*(10), 1376-1382. doi:10.4088/JCP.09m05888blu

Cruccu, G., Aziz, T. Z., Garcia-Larrea, L., Hansson, P., Jensen, T. S., Lefaucheur, J. -., Simpson, B. A., & Taylor, R. S. (2007). EFNS guidelines on neurostimulation therapy for neuropathic pain. *European Journal of Neurology, 14*(9), 952-970. doi:10.1111/j.1468-1331.2007.01916.x

Cruccu, G., Garcia Larrea, L., Hansson, P., Keindl, M., Lefaucheur, J., Paulus, W., Taylor, R., Tronnier, V., Truini, A., & Attal, N. (2016). EAN guidelines on central neurostimulation therapy in chronic pain conditions. *European Journal of Neurology, 23*(10), 1489-1499. doi:10.1111/ene.13103

Daskalakis, Z. J., Moeller, B., Christensen, B. K., Fitzgerald, P. B., Gunraj, C., & Chen, R. (2006). The effects of repetitive transcranial magnetic stimulation on cortical inhibition in healthy human subjects. *Experimental Brain Research, 174*(3), 403-412. doi:10.1007/s00221-006-0472-0

Davies, E., Knox, E., & Donaldson, I. (1994). The usefulness of nimodipine, an L-calcium channel antagonist, in the treatment of tinnitus. *British Journal of Audiology, 28*(3), 125-129. doi:10.3109/03005369409086559

Davila Pérez, P., Jannati, A., Fried, P., Cudeiro Mazaira, J., & Pascual Leone, A. (2018). The effects of waveform and current direction on the efficacy and test-retest reliability of transcranial magnetic stimulation. *Neuroscience, 393*, 97-109. doi:10.1016/j.neuroscience.2018.09.044

de Azevedo, A. A., Langguth, B., de Oliveira, P. M., & Figueiredo, R. R. (2009). Tinnitus treatment with piribedil guided by electrocochleography and acoustic otoemissions. *Otology & Neurotology, 30*(5), 676-680. doi:10.1097/MAO.0b013e3181ab8fd5

de Azevedo, A., & Figueiredo, R. (2007). Treatment of tinnitus with acamprosate. *Prog Brain Res, 166*, 273-277. doi:10.1016/S0079-6123(07)66025-7

De Ridder, D., De Mulder, G., Verstraeten, E., Van der Kelen, K., Sunaert, S., Smits, M., Kovacs, S., Verlooy, J., Van de Heyning, P., & Moller, A. R. (2006). Primary and secondary auditory cortex stimulation for intractable tinnitus. *Orl-Journal for Oto-Rhino-Laryngology and its Related Specialties, 68*(1), 48-54. doi:10.1159/000090491

De Ridder, D., De Mulder, G., Walsh, V., Muggleton, N., Sunaert, S., & Moller, A. (2004). Magnetic and electrical stimulation of the auditory cortex for intractable tinnitus - case report. *Journal of Neurosurgery, 100*(3), 560-564. doi:10.3171/jns.2004.100.3.0560

De Ridder, D., Verstraeten, E., Van der Kelen, K., De Mulder, G., Sunaert, S., Verlooy, J., Van de Heyning, P., & Moller, A. (2005). Transcranial magnetic stimulation for tinnitus: Influence of tinnitus duration on stimulation parameter choice and maximal tinnitus suppression. *Otology & Neurotology, 26*(4), 616-619. doi:10.1097/01.mao.0000178146.91139.3c

De Ridder, D., Elgoyhen, A. B., Romo, R., & Langguth, B. (2011a). Phantom percepts: Tinnitus and pain as persisting aversive memory networks. *Proceedings of the National Academy of Sciences of the United States of America, 108*(20), 8075-8080. doi:10.1073/pnas.1018466108

De Ridder, D., Joos, K., & Vanneste, S. (2016). Anterior cingulate implants for tinnitus: Report of 2 cases. *Journal of Neurosurgery, 124*(4), 893-901. doi:10.3171/2015.3.JNS142880

De Ridder, D., Kilgard, M., Engineer, N., & Vanneste, S. (2015). Placebo-controlled vagus nerve stimulation paired with tones in a patient with refractory tinnitus: A case report. *Otology & Neurotology, 36*(4), 575-580.

De Ridder, D., Perera, S., & Vanneste, S. (2017). State of the art: Novel applications for cortical stimulation. *Neuromodulation, 20*(3), 206-214. doi:10.1111/ner.12593

De Ridder, D., Vanneste, S., Engineer, N. D., & Kilgard, M. P. (2014a). Safety and efficacy of vagus nerve stimulation PairedWith tones for the treatment of tinnitus: A case series. *Neuromodulation, 17*(2), 170-179. doi:10.1111/ner.12127

De Ridder, D., Vanneste, S., & Freeman, W. (2014b). The bayesian brain: Phantom percepts resolve sensory uncertainty. *Neuroscience and Biobehavioral Reviews, 44*, 4-15. doi:10.1016/j.neubiorev.2012.04.001

De Ridder, D., Vanneste, S., Kovacs, S., Sunaert, S., Menovsky, T., van de Heyning, P., & Moller, A. (2011b). Transcranial magnetic stimulation and extradural electrodes implanted on secondary auditory cortex for tinnitus suppression clinical article. *Journal of Neurosurgery, 114*(4), 903-911. doi:10.3171/2010.11.JNS10197

De Ridder, D., Vanneste, S., Plazier, M., Menovsky, T., van de Heyning, P., Kovacs, S., & Sunaert, S. (2012). Dorsolateral prefrontal cortex transcranial magnetic stimulation and electrode implant for intractable tinnitus. *World Neurosurgery, 77*(5-6), 778-784. doi:10.1016/j.wneu.2011.09.009

De Ridder, D., Vanneste, S., Weisz, N., Londero, A., Schlee, W., Belen Elgoyhen, A., & Langguth, B. (2014c). An integrative model of auditory phantom perception: Tinnitus as a unified percept of interacting separable subnetworks. *Neuroscience and Biobehavioral Reviews, 44*, 16-32. doi:10.1016/j.neubiorev.2013.03.021

Dehkordi, M. A., Abolbashari, S., Taheri, R., & Einolghozati, S. (2011). Efficacy of gabapentin on subjective idiopathic tinnitus: A randomized, double-blind, placebo-controlled trial. *Ent-Ear Nose & Throat Journal, 90*(4), +.

Dehkordi, M. A., Einolghozati, S., Ghasemi, S. M., Abolbashari, S., Meshkat, M., & Behzad, H. (2015). Effect of low-level laser therapy in the treatment of cochlear tinnitus: A double-blind, placebo-controlled study. *Ent-Ear Nose & Throat Journal, 94*(1), 32-36.

Del Bo, L., & Ambrosetti, U. (2007). Hearing aids for the treatment of tinnitus. *Tinnitus: Pathophysiology and Treatment, 166*, 341-345. doi:10.1016/S0079-6123(07)66032-4

Demirkol, N., Usumez, A., Demirkol, M., Sari, F., & Akcaboy, C. (2017). Efficacy of low-level laser therapy in subjective tinnitus patients with temporomandibular disorders. *Photomedicine and Laser Surgery, 35*(8), 427-431. doi:10.1089/pho.2016.4240

Derogatis, L. R. (Ed.). (1977). *SCL-90: Administration, scoring and procedure manual-I for the revised version*. Baltimore: John Hopkins University, School of Medicine, Clinical Psychometric Unit.

Di Lazzaro, V., Dileone, M., Pilato, F., Capone, F., Musumeci, G., Ranieri, F., Ricci, V., Bria, P., Di Iorio, R., de Waure, C., Pasqualetti, P., & Profice, P. (2011). Modulation of motor cortex neuronal networks by rTMS: Comparison of local and remote effects of six different protocols of stimulation. *Journal of Neurophysiology, 105*(5), 2150-2156. doi:10.1152/jn.00781.2010

Di Lazzaro, V., Oliviero, A., Pilato, F., Mazzone, P., Insola, A., Ranieri, F., & Tonali, P. A. (2003). Corticospinal volleys evoked by transcranial stimulation of the brain in conscious humans. *Neurological Research, 25*(2), 143-150. doi:10.1179/016164103101201292

Dib, G., Kasse, C., Alves de Andrade, T., Gurgel Testa, J., & Cruz, O. L. M. (2007). Tinnitus treatment with trazodone. *Brazilian Journal of Otorhinolaryngology, 73*(3), 390-397.

Dietrich, S., Smith, J., Scherzinger, C., Hofmann-Preiss, K., Freitag, T., Eisenkolb, A., & Ringler, R. (2008). A novel transcutaneous vagus nerve stimulation leads to brainstem and cerebral activations measured by functional MRI. *Biomedizinische Technik, 53*(3), 104-111. doi:10.1515/BMT.2008.022

Dobie, R. A. (2003). Depression and tinnitus. *Otolaryngologic Clinics of North America, 36*(2), 383-8. doi:10.1016/S0030-6665(02)00168-8

Dobie, R. A., Sakai, C. S., Sullivan, M. D., Katon, W. J., & Russo, J. (1993). Antidepressant treatment of tinnitus patients - report of a randomized clinical-trial and clinical-prediction of benefit. *American Journal of Otology, 14*(1), 18-23.

Du, X., & Jansen, B. H. (2011). A neural network model of normal and abnormal auditory information processing. *Neural Networks, 24*(6), 568-574. doi:10.1016/j.neunet.2011.03.002

Dudek, S. M., & Bear, M. F. (1992). Homosynaptic long-term depression in area Ca1 of hippocampus and effects of N-methyl-D-aspartate receptor blockade. *Proceedings of the National Academy of Sciences of the United States of America, 89*(10), 4363-4367. doi:10.1073/pnas.89.10.4363

Dworkin, R. H., Turk, D. C., Wyrwich, K. W., Beaton, D., Cleeland, C. S., Farrar, J. T., Haythornthwaite, J. A., Jensen, M. P., Kerns, R. D., Ader, D. N., Brandenburg, N., Burke, L. B., Cella, D., Chandler, J., Cowan, P., Dimitrova, R., Dionne, R., Hertz, S., Jadad, A. R., Katz, N. P., Kehlet, H., Kramer, L. D., Manning, D. C., McCormick, C., McDermott, M. P., McQuay, H. J., Patel, S., Porter, L., Quessy, S., Rappaport, B. A., Rauschkolb, C., Revickl, D. A., Rothman, M., Schmader, K. E., Stacey, B. R., Stauffer, J. W., Von Stein, T., White, R. E., Witter, J., & Zavislc, S. (2008). Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *Journal of Pain, 9*(2), 105-121. doi:10.1016/j.jpain.2007.09.005

Eggermont, J. J., & Komiya, H. (2000). Moderate noise trauma in juvenile cats results in profound cortical topographic map changes in adulthood. *Hearing Research, 142*(1-2), 89-101. doi:10.1016/S0378-5955(00)00024-1

Eichhammer, P., Langguth, B., Marienhagen, J., Kleinjung, T., & Hajak, G. (2003). Neuronavigated repetitive transcranial magnetic stimulation in patients with tinnitus: A short case series. *Biological Psychiatry, 54*(8), 862-865. doi:10.1016/S0006-3223(03)01896-6

Eisenman, D. J., & Teplitzky, T. B. (2016). *Surgical treatment of tinnitus* doi://dx.doi.org.ezproxy.utu.fi/10.1016/j.nic.2015.12.010

Elzayat, S., El-Sherif, H., Hegazy, H., Gabr, T., & El-Tahan, A. (2016). Tinnitus: Evaluation of intratympanic injection of combined lidocaine and corticosteroids. *Orl-Journal for Oto-Rhino-Laryngology Head and Neck Surgery, 78*(3), 159-166. doi:10.1159/000445774

Engineer, N. D., Moller, A. R., & Kilgard, M. P. (2013). Directing neural plasticity to understand and treat tinnitus. *Hearing Research, 295*, 58-66. doi:10.1016/j.heares.2012.10.001

Erlandsson, S., & Persson, M. (2006). A longitudinal study investigating the contribution of mental illness in chronic tinnitus patients. *Audiol Med, 4*, 124-133.

Estola-Partanen, M. (2000). *Muscular tension and tinnitus: An experimental trial of trigger point injections on tinnitus* Retrieved from http://tampub.uta.fi/handle/10024/67059

Figueiredo, R. R., Rates, M. A., de Azevedo, A. A., de Oliveira, P. M., & de Navarro, Patricia B A. (2010). Correlation analysis of hearing thresholds, validated questionnaires and psychoacoustic measurements in tinnitus patients. *Brazilian Journal of Otorhinolaryngology, 76*(4), 522-526.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. (Eds.). (1997a). *Structured clinical interview for DSM-IV axis i disorders (SCID-I, 4/97 version)*. New York, NY: Biometrics Research Department, New York State Psychiatric Institute.

First, M., Spitzer, R., Gibbon, M., Williams, J., & Benjamin, L. (Eds.). (1997b). *Structured clinical interview*

for DSM-IV axis II disorders (SCID-II). New York, NY: Biometrics Research Department, New York State Psychiatric Institute.

Fitzgerald, P. B., Hoy, K., McQueen, S., Maller, J. J., Herring, S., Segrave, R., Bailey, M., Been, G., Kulkarni, J., & Daskalakis, Z. J. (2009). A randomized trial of rTMS targeted with MRI based neuro-navigation in treatment-resistant depression. *Neuropsychopharmacology, 34*(5), 1255-1262. doi:10.1038/npp.2008.233

Flor, H., Elbert, T., Knecht, S., Wienbruch, C., Pantev, C., Birbaumer, N., Larbig, W., & Taub, E. (1995). Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. *Nature, 375*(6531), 482-484. doi:10.1038/375482a0

Folmer, R. L., Griest, S. E., & Martin, W. H. (2001). Chronic tinnitus as phantom auditory pain. *Otolaryngology-Head and Neck Surgery, 124*(4), 394-400. doi:10.1067/mhn.2001.114673

Folmer, R. L., Theodoroff, S. M., Casiana, L., Shi, Y., Griest, S., & Vachhani, J. (2015). Repetitive transcranial magnetic stimulation treatment for chronic tinnitus: A randomized clinical trial. *JAMA Otolaryngology-- Head & Neck Surgery, 141*(8), 716-22. doi:10.1001/jamaoto.2015.1219

Folmer, R. L., Theodoroff, S. M., Martin, W. H., & Shi, Y. (2014). Experimental, controversial, and futuristic treatments for chronic tinnitus. *Journal of the American Academy of Audiology, 25*(1), 106-125. doi:10.3766/jaaa.25.1.7

Folmer, R., Griest, S., & Martin, W. (2008). Obsessive-compulsiveness in a population of tinnitus patients. *The International Tinnitus Journal, 14*(2), 127-130.

Forogh, B., Mirshaki, Z., Raissi, G. R., Shirazi, A., Mansoori, K., & Ahadi, T. (2016). Repeated sessions of transcranial direct current stimulation for treatment of chronic subjective tinnitus: A pilot randomized controlled trial. *Neurological Sciences, 37*(2), 253-259. doi:10.1007/s10072-015-2393-9

Fox, P., Ingham, R., George, M. S., Mayberg, H., Ingham, J., Roby, J., Martin, C., & Jerabek, P. (1997). Imaging human intra-cerebral connectivity by PET during TMS. *Neuroreport, 8*(12), 2787-2791. doi:10.1097/00001756-199708180-00027

Fuggetta, G., & Noh, N. A. (2013). A neurophysiological insight into the potential link between transcranial magnetic stimulation, thalamocortical dysrhythmia and neuropsychiatric disorders. *Experimental Neurology, 245*, 87-95. doi:10.1016/j.expneurol.2012.10.010

Gamboa, O. L., Antal, A., Moliadze, V., & Paulus, W. (2010). Simply longer is not better: Reversal of theta burst after-effect with prolonged stimulation. *Experimental Brain Research, 204*(2), 181-187. doi:10.1007/s00221-010-2293-4

Geocze, L., Mucci, S., Abranches, D. C., de Marco, M. A., & Penido, N. d. O. (2013). Systematic review on the evidences of an association between tinnitus and depression. *Brazilian Journal of Otorhinolaryngology, 79*(1), 106-111. doi:10.5935/1808-8694.20130018

Goebel, G., Kahl, M., Arnold, W., & Fichter, M. (2006). 15-year prospective follow-up study of behavioral therapy in a large sample of inpatients with chronic tinnitus. *Acta Oto-Laryngologica, 126*, 70-79. doi:10.1080/03655230600895267

Greenwell, K., Sereda, M., Coulson, N., El Refaie, A., & Hoare, D. J. (2016). A systematic review of techniques and effects of self-help interventions for tinnitus: Application of taxonomies from health psychology. *International Journal of Audiology, 55*, S89. doi:10.3109/14992027.2015.1137363

Groppa, S., Oliviero, A., Eisen, A., Quartarone, A., Cohen, L. G., Mall, V., Kaelin-Lang, A., Mima, T., Rossi, S., Thickbroom, G. W., Rossini, P. M., Ziemann, U., Valls-Sole, J., & Siebner, H. R. (2012). A practical guide to diagnostic transcranial magnetic stimulation: Report of an IFCN committee. *Clinical Neurophysiology, 123*(5), 858-882. doi:10.1016/j.clinph.2012.01.010

Gülick-Bailer, M. v. (1995). *Schedules for clinical assessment in neuropsychiatry*. Bern u.a: Huber.

Gungor, A., Dogru, S., Cincik, H., Erkul, E., & Poyrazoglu, E. (2008). Effectiveness of transmeatal low power laser irradiation for chronic tinnitus. *Journal of Laryngology and Otology, 122*(5), 447-451. doi:10.1017/S0022215107009619

Hagelberg, N., Jaaskelainen, S. K., Martikainen, I. K., Mansikka, H., Forssell, H., Harry, S. F., Hietala,

G., & Pertovaara, A. (2004). Striatal dopamine D2 receptors in modulation of pain in humans: A review. *European Journal of Pharmacology, 500*(1-3), 187-192. doi:10.1016/j.ejphar.2004.07.024

Hamada, M., Murase, N., Hasan, A., Balaratnam, M., & Rothwelll, J. C. (2013). The role of interneuron networks in driving human motor cortical plasticity. *Cerebral Cortex, 23*(7), 1593-1605. doi:10.1093/cercor/bhs147

Han, S., Nam, E., Won, J. Y., Lee, K. U., Chun, W., Choi, H. K., & Levine, R. A. (2012). Clonazepam quiets tinnitus: A randomised crossover study with ginkgo biloba. *Journal of Neurology Neurosurgery and Psychiatry, 83*(8), 821-827. doi:10.1136/jnnp-2012-302273

Hannah, R., & Rothwell, J. C. (2017). Pulse duration as well as current direction determines the specificity of transcranial magnetic stimulation of motor cortex during contraction. *Brain Stimulation, 10*(1), 106-115. doi:10.1016/j.brs.2016.09.008

Harrop-Griffiths, J., Katon, W., Dobie, R., Sakai, C., & Russo, J. (1987). Chronic tinnitus - association with psychiatric diagnoses. *Journal of Psychosomatic Research, 31*(5), 613-621. doi:10.1016/0022-3999(87)90040-7

He, M., Li, X., Liu, Y., Zhong, J., Jiang, L., Liu, Y., Chen, Q., Xie, Y., & Zhang, Q. (2016). Electroacupuncture for tinnitus: A systematic review. *Plos One, 11*(3), e0150600. doi:10.1371/journal.pone.0150600

Henry, J. A., Dennis, K. C., & Schechter, M. A. (2005). General review of tinnitus: Prevalence, mechanisms, effects, and management. *Journal of Speech Language and Hearing Research, 48*(5), 1204-1235. doi:10.1044/1092-4388(2005/084)

Henry, J. A., Roberts, L. E., Caspary, D. M., Theodoroff, S. M., & Salvi, R. J. (2014). Underlying mechanisms of tinnitus: Review and clinical implications. *Journal of the American Academy of Audiology, 25*(1), 5-22. doi:10.3766/jaaa.25.1.2

Henry, J. A., Schechter, M. A., Zaugg, T. L., Griest, S., Jastreboff, P. J., Vernon, J. A., Kaelin, C., Meikle, M. B., Lyons, K. S., & Stewart, B. J. (2006). Outcomes of clinical trial: Tinnitus masking versus tinnitus retraining therapy. *Journal of the American Academy of Audiology, 17*(2), 104-132. doi:10.3766/jaaa.17.2.4

Hertzano, R., Teplitzky, T. B., & Eisenman, D. J. (2016). Clinical evaluation of tinnitus. *Neuroimaging Clinics of North America, 26*(2), +. doi:10.1016/j.nic.2015.12.004

Hesser, H., Weise, C., Westin, V. Z., & Andersson, G. (2011). A systematic review and meta-analysis of randomized controlled trials of cognitive-behavioral therapy for tinnitus distress. *Clinical Psychology Review, 31*(4), 545-553. doi:10.1016/j.cpr.2010.12.006

Hilton, M. P., Zimmermann, E. F., & Hunt, W. T. (2013). Ginkgo biloba for tinnitus. *Cochrane Database of Systematic Reviews,* (3), CD003852. doi:10.1002/14651858.CD003852.pub3

Hoare, D. J., Adjamian, P., & Sereda, M. (2016). Electrical stimulation of the ear, head, cranial nerve, or cortex for the treatment of tinnitus: A scoping review. *Neural Plasticity,* , 5130503. doi:10.1155/2016/5130503

Hoare, D. J., Edmondson-Jones, M., Sereda, M., Akeroyd, M. A., & Hall, D. (2014). Amplification with hearing aids for patients with tinnitus and co-existing hearing loss. *Cochrane Database of Systematic Reviews,* (1), CD010151. doi:10.1002/14651858.CD010151.pub2

Hobson, J., Chisholm, E., & El Refaie, A. (2012). Sound therapy (masking) in the management of tinnitus in adults. *Cochrane Database of Systematic Reviews,* (11), CD006371. doi:10.1002/14651858.CD006371.pub3

Hoekstra, C. E., Versnel, H., Neggers, S. F., Niesten, M. E., & van Zanten, G. A. (2013). Bilateral low-frequency repetitive transcranial magnetic stimulation of the auditory cortex in tinnitus patients is not effective: A randomised controlled trial. *Audiology & Neuro-Otology, 18*(6), 362-373. doi:10.1159/000354977 [doi]

Hoekstra, C. E. L., Rynja, S. P., van Zanten, G. A., & Rovers, M. M. (2011). Anticonvulsants for tinnitus. *Cochrane Database of Systematic Reviews,* (7), CD007960. doi:10.1002/14651858.CD007960.pub2

Holgers, K. M., Zoger, S., & Svedlund, K. (2005). Predictive factors for development of severe tinnitus suffering-further characterisation. *International Journal of Audiology, 44*(10), 584-592.

doi:10.1080/14992020500190235

Holi, M. M., Sammallahti, P. R., & Aalberg, V. A. (1998). A finnish validation study of the SCL-90. *Acta Psychiatrica Scandinavica, 97*(1), 42-46. doi:10.1111/j.1600-0447.1998.tb09961.x

Hoogendam, J. M., Ramakers, G. M. J., & Di Lazzaro, V. (2010). Physiology of repetitive transcranial magnetic stimulation of the human brain. *Brain Stimulation, 3*(2), 95-118. doi:10.1016/j.brs.2009.10.005

Houdayer, E., Degardin, A., Cassim, F., Bocquillon, P., Derambure, P., & Devanne, H. (2008). The effects of low- and high-frequency repetitive TMS on the input/output properties of the human corticospinal pathway. *Experimental Brain Research, 187*(2), 207-217. doi:10.1007/s00221-008-1294-z

Houze, B., Bradley, C., Magnin, M., & Garcia-Larrea, L. (2013). Changes in sensory hand representation and pain thresholds induced by motor cortex stimulation in humans. *Cerebral Cortex, 23*(11), 2667-2676. doi:10.1093/cercor/bhs255

Hurtuk, A., Dome, C., Holloman, C. H., Wolfe, K., Welling, D. B., Dodson, E. E., & Jacob, A. (2011). Melatonin: Can it stop the ringing? *Annals of Otology Rhinology and Laryngology, 120*(7), 433-440.

Hyvärinen, P., Mäkitie, A., & Aarnisalo, A. A. (2016). Self-administered domiciliary tDCS treatment for tinnitus: A double-blind sham-controlled study. *Plos One, 11*(4), e0154286. doi:10.1371/journal.pone.0154286

Hyvärinen, P., Yrttiaho, S., Lehtimäki, J., Ilmoniemi, R. J., Makitie, A., Ylikoski, J., Makela, J. P., & Aarnisalo, A. A. (2015). Transcutaneous vagus nerve stimulation modulates tinnitus-related beta- and gamma-band activity. *Ear and Hearing, 36*(3), E85.

International Organisation for Standardization. (1998). *Acoustics - audiometric test methods - part 1: Basic pure tone air and bone conduction threshold audiometry (ISO 8253-1:1989)*

International Organisation for Standardization. (2000). *Acoustics - reference zero for the calibration of audiometric equipment - part 1: Reference equivalent threshold sound pressure levels for pure tones and supra-aural earphones (ISO 389-1:1998)*

Jääskeläinen, S. K., Lindholm, P., Valmunen, T., Pesonen, U., Taiminen, T., Virtanen, A., Lamusuo, S., Forssell, H., Hagelberg, N., Hietala, J., & Pertovaara, A. (2014). Variation in the dopamine D2 receptor gene plays a key role in human pain and its modulation by transcranial magnetic stimulation. *Pain, 155*(10), 2180-2187. doi:10.1016/j.pain.2014.08.029

Jackson, P. (1985). A comparison of the effects of 8th nerve-section with lidocaine on tinnitus. *Journal of Laryngology and Otology, 99*(7), 663-666. doi:10.1017/S0022215100097449

Jalali, M. M., Kousha, A., Naghavi, S. E., Soleimani, R., & Banan, R. (2009). The effects of alprazolam on tinnitus: A cross-over randomized clinical trial. *Medical Science Monitor, 15*(11), PI60.

James, A. L., & Burton, M. J. (2001). Betahistine for menire's disease or syndrome. *Cochrane Database of Systematic Reviews,* (1), CD001873. doi:10.1002/14651858.CD001873

Jarcho, J. M., Mayer, E. A., Jiang, Z. K., Feier, N. A., & London, E. D. (2012). Pain, affective symptoms, and cognitive deficits in patients with cerebral dopamine dysfunction. *Pain, 153*(4), 744-754. doi:10.1016/j.pain.2012.01.002

Jastreboff, P. J. (1990). Phantom auditory-perception (tinnitus) - mechanisms of generation and perception. *Neuroscience Research, 8*(4), 221-254. doi:10.1016/0168-0102(90)90031-9

Jastreboff, P. J. (2015). 25 years of tinnitus retraining therapy. *Hno, 63*(4), 307-311. doi:10.1007/s00106-014-2979-1

Jastreboff, P. J., & Hazell, J. (1999). Tinnitus retraining therapy. *British Journal of Audiology, 33*(1), 68-69.

Jastreboff, P. J., & Jastreboff, M. M. (2006). Tinnitus retraining therapy: A different view on tinnitus. *Orl-Journal for Oto-Rhino-Laryngology and its Related Specialties, 68*(1), 23-29. doi:10.1159/000090487

Jenkins, C. D., Stanton, B. A., Niemcryk, S. J., & Rose, R. M. (1988). A scale for the estimation of sleep problems in clinical research. *Journal of Clinical Epidemiology, 41*(4), 313-321. doi:10.1016/0895-4356(88)90138-2

Johnson, R. M., Brummett, R., & Schleuning, A. (1993). Use of alprazolam for relief of tinnitus - a double-blind-study. *Archives of Otolaryngology-Head & Neck Surgery, 119*(8), 842-845.

Juckel, G., Molnar, M., Hegerl, U., Csepe, V., & Karmos, G. (1997). Auditory-evoked potentials as indicator of brain serotonergic activity - first evidence in behaving cats. *Biological Psychiatry, 41*(12), 1181-1195. doi:10.1016/S0006-3223(96)00240-5

Jufas, N. E., & Wood, R. (2015). The use of benzodiazepines for tinnitus: Systematic review. *The Journal of Laryngology and Otology, 129 Suppl 3*, S22. doi:10.1017/S0022215115000808

Kammer, T., Beck, S., Erb, M., & Grodd, W. (2001). The influence of current direction on phosphene thresholds evoked by transcranial magnetic stimulation. *Clinical Neurophysiology, 112*(11), 2015-2021. doi:10.1016/S1388-2457(01)00673-3

Keck, M. E., Welt, T., Muller, M. B., Erhardt, A., Ohl, F., Toschi, N., Holsboer, F., & Sillaber, I. (2002). Repetitive transcranial magnetic stimulation increases the release of dopamine in the mesolimbic and mesostriatal system. *Neuropharmacology, 43*(1), 101-109. doi:10.1016/S0028-3908(02)00069-2

Kedzior, K. K., Azorina, V., & Reitz, S. K. (2014). More female patients and fewer stimuli per session are associated with the short-term antidepressant properties of repetitive transcranial magnetic stimulation (rTMS): A meta-analysis of 54 sham-controlled studies published between 1997-2013. *Neuropsychiatric Disease and Treatment, 10*, 727-756. doi:10.2147/NDT.S58405

Keeser, D., Meindl, T., Bor, J., Palm, U., Pogarell, O., Mulert, C., Brunelin, J., Moeller, H., Reiser, M., & Padberg, F. (2011). Prefrontal transcranial direct current stimulation changes connectivity of resting-state networks during fMRI. *Journal of Neuroscience, 31*(43), 15284-15293. doi:10.1523/JNEUROSCI.0542-11.2011

Kessler, R. C., Berglund, P., Demler, O., Jin, R., & Walters, E. E. (2005a). Lifetime prevalence and age-of-onset distributions' of DSM-IV disorders in the national comorbidity survey replication. *Archives of General Psychiatry, 62*(6), 593-602. doi:10.1001/archpsyc.62.6.593

Kessler, R. C., Chiu, W. T., Demler, O., & Walters, E. E. (2005b). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the national comorbidity survey replication. *Archives of General Psychiatry, 62*(6), 617-627. doi:10.1001/archpsyc.62.6.617

Kessler, R. C., Chiu, W. T., Jin, R., Ruscio, A. M., Shear, K., & Walters, E. E. (2006). The epidemiology of panic attacks, panic disorder, and agoraphobia in the national comorbidity survey replication. *Archives of General Psychiatry, 63*(4), 415-424. doi:10.1001/archpsyc.63.4.415

Khedr, E. M., Rothwell, J. C., Ahmed, M. A., & El-Atar, A. (2008). Effect of daily repetitive transcranial magnetic stimulation for treatment of tinnitus: Comparison of different stimulus frequencies. *Journal of Neurology Neurosurgery and Psychiatry, 79*(2), 212. doi:10.1136/jnnp.2007.127712

Kilgard, M. P., & Merzenich, M. M. (1998a). Cortical map reorganization enabled by nucleus basalis activity. *Science, 279*(5357), 1714-1718. doi:10.1126/science.279.5357.1714

Kilgard, M. P., & Merzenich, M. M. (1998b). Plasticity of temporal information processing in the primary auditory cortex. *Nature Neuroscience, 1*(8), 727-731. doi:10.1038/3729

Kim, D., Park, S., Park, K., Choi, H. G., Jeon, E., Park, Y., & Yeo, S. W. (2011). Clinical characteristics and audiological significance of spontaneous otoacoustic emissions in tinnitus patients with normal hearing. *Journal of Laryngology and Otology, 125*(3), 246-250. doi:10.1017/S0022215110002380

Kim, J., Choi, J., Lee, D., Choi, T., Lee, M. S., & Ernst, E. (2012). Acupuncture for the treatment of tinnitus: A systematic review of randomized clinical trials. *Bmc Complementary and Alternative Medicine, 12*, 97. doi:10.1186/1472-6882-12-97

Kleinjung, T., Eichhammer, P., Langguth, B., Jacob, P., Marienhagen, J., Hajak, G., Wolf, S. R., & Strutz, J. (2005). Long-term effects of repetitive transcranial magnetic stimulation (rTMS) in patients with chronic tinnitus. *Otolaryngology-Head and Neck Surgery, 132*(4), 566-569. doi:10.1016/j.otohns.2004.09.134

Kleinjung, T., Steffens, T., Sand, P., Murthum, T., Hajak, G., Strutz, J., Langguth, B., & Eichhammer, P. (2007). Which tinnitus patients benefit from transcranial magnetic stimulation? *Otolaryngology-Head and Neck Surgery, 137*(4), 589-595. doi:10.1016/j.otohns.2006.12.007

Kraus, T., Hoesl, K., Kiess, O., Schanze, A., Kornhuber, J., & Forster, C. (2007). BOLD fMRI deactivation of limbic and temporal brain structures and mood enhancing effect by transcutaneous vagus nerve stimulation. *Journal of Neural Transmission, 114*(11), 1485-1493. doi:10.1007/s00702-007-0755-z

Kreuzer, P. M., Landgrebe, M., Resch, M., Husser, O., Schecklmann, M., Geisreiter, F., Poeppl, T. B., Prasser, S. J., Hajak, G., Rupprecht, R., & Langguth, B. (2014). Feasibility, safety and efficacy of transcutaneous vagus nerve stimulation in chronic tinnitus: An open pilot study. *Brain Stimulation, 7*(5), 740-747. doi:10.1016/j.brs.2014.05.003

Kreuzer, P., Poeppl, T., Rupprecht, R., Vielsmeier, V., Lehner, A., Langguth, B., & Schecklmann, M. (2017). Individualized repetitive transcranial magnetic stimulation treatment in chronic tinnitus? *Frontiers in Neurology, 8*, 126. doi:10.3389/fneur.2017.00126

Krog, N. H., Engdahl, B., & Tambs, K. (2010). The association between tinnitus and mental health in a general population sample: Results from the HUNT study. *Journal of Psychosomatic Research, 69*(3), 289-298. doi:10.1016/j.jpsychores.2010.03.008

Kumar, R., Lozano, A. M., Kim, Y. J., Hutchison, W. D., Sime, E., Halket, E., & Lang, A. E. (1998). Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced parkinson's disease. *Neurology, 51*(3), 850-855.

Lainez, M. J. A., & Piera, A. (2007). Botulinum toxin for the treatment of somatic tinnitus. *Tinnitus: Pathophysiology and Treatment, 166*, 335-338. doi:10.1016/S0079-6123(07)66031-2

Lambert, G., Johansson, M., Agren, H., & Friberg, P. (2000). Reduced brain norepinephrine and dopamine release in treatment-refractory depressive illness - evidence in support of the catecholamine hypothesis of mood disorders. *Archives of General Psychiatry, 57*(8), 787-793. doi:10.1001/archpsyc.57.8.787

Lamusuo, S., Hirvonen, J., Lindholm, P., Martikainen, I. K., Hagelberg, N., Parkkola, R., Taiminen, T., Hietala, J., Helin, S., Virtanen, A., Pertovaara, A., & Jääskeläinen, S. K. (2017). Neurotransmitters behind pain relief with transcranial magnetic stimulation - positron emission tomography evidence for release of endogenous opioids. *European Journal of Pain,* doi:10.1002/ejp.1052

Landgrebe, M., Hajak, G., Wolf, S., Padberg, F., Klupp, P., Fallgatter, A. J., Polak, T., Hoeppner, J., Haker, R., Cordes, J., Klenzner, T., Schoenfeldt-Lecuona, C., Kammer, T., Graf, E., Koller, M., Kleinjung, T., Lehner, A., Schecklmann, M., Poeppl, T. B., Kreuzer, P., Frank, E., & Langguth, B. (2017). 1-hz rTMS in the treatment of tinnitus: A sham-controlled, randomized multicenter trial. *Brain Stimulation, 10*(6), 1112-1120. doi:10.1016/j.brs.2017.08.001

Landgrebe, M., Langguth, B., Rosengarth, K., Braun, S., Koch, A., Kleinjung, T., May, A., de Ridder, D., & Hajak, G. (2009). Structural brain changes in tinnitus: Grey matter decrease in auditory and non-auditory brain areas. *NeuroImage, 46*(1), 213-218. doi:10.1016/j.neuroimage.2009.01.069

Langguth, B., Goodey, R., Azevedo, A., Bjorne, A., Cacace, A., Crocetti, A., Del Bo, L., De Ridder, D., Diges, I., Elbert, T., Flor, H., Herraiz, C., Ganz Sanchez, T., Eichhammer, P., Figueiredo, R., Hajak, G., Kleinjung, T., Landgrebe, M., Londero, A., Lainez, M. J. A., Mazzoli, M., Meikle, M. B., Melcher, J., Rauschecker, J. P., Sand, P. G., Struve, M., Van de Heyning, P., Van Dijk, P., & Vergara, R. (2007a). Consensus for tinnitus patient assessment and treatment outcome measurement: Tinnitus research initiative meeting, regensburg, july 2006. *Tinnitus: Pathophysiology and Treatment, 166*, 525-536. doi:10.1016/S0079-6123(07)66050-6

Langguth, B., Kleinjung, T., Fischer, B., Hajak, G., Eichhammer, P., & Sand, P. G. (2007b). Tinnitus severity, depression, and the big five personality traits. *Tinnitus: Pathophysiology and Treatment, 166*, 221-225. doi:10.1016/S0079-6123(07)66020-8

Langguth, B., Kleinjung, T., Landgrebe, M., de Ridder, D., & Hajak, G. (2010). rTMS for the treatment of tinnitus: The role of neuronavigation for coil positioning. *Neurophysiologie Clinique = Clinical Neurophysiology, 40*(1), 45-58. doi:10.1016/j.neucli.2009.03.001 [doi]

Langguth, B., Landgrebe, M., Frank, E., Schecklmann, M., Sand, P. G., Vielsmeier, V., Hajak, G., & Kleinjung, T. (2014). Efficacy of different protocols of transcranial magnetic stimulation for the treatment of tinnitus: Pooled analysis of two randomized controlled studies. *World Journal of Biological Psychiatry, 15*(4), 276-285. doi:10.3109/15622975.2012.708438

Langguth, B., de Ridder, D., Dornhoffer, J. L., Eichhammer, P., Folmer, R. L., Frank, E., Fregni, F., Gerloff, C., Khedr, E., Kleinjung, T., Landgrebe, M., Lee, S., Lefaucheur, J., Londero, A., Marcondes, R., Moller, A. R., Pascual-Leone, A., Plewnia, C., Rossi, S., Sanchez, T., Sand, P., Schlee, W., Pysch, D., Steffens, T., van de Heyning, P., & Hajak, G. (2008). Controversy: Does repetitive transcranial magnetic stimulation/transcranial direct current stimulation show efficacy in treating tinnitus patients? *Brain Stimulation, 1*(3), 192-205. doi:10.1016/j.brs.2008.06.003

Langguth, B., Kreuzer, P. M., Kleinjung, T., & De Ridder, D. (2013). Tinnitus: Causes and clinical management. *Lancet Neurology, 12*(9), 920-930.

Langguth, B., Landgrebe, M., Kleinjung, T., Sand, G. P., & Hajak, G. (2011). Tinnitus and depression. *World Journal of Biological Psychiatry, 12*(7), 489-500. doi:10.3109/15622975.2011.575178

Langguth, B., Zowe, M., Landgrebe, M., Sand, P., Kleinjung, T., Binder, H., Hajak, G., & Eichhammer, P. (2006). Transcranial magnetic stimulation for the treatment of tinnitus: A new coil positioning method and first results. *Brain Topography, 18*(4), 241-247. doi:10.1007/s10548-006-0002-1

Lanting, C. P., de Kleine, E., & van Dijk, P. (2009). Neural activity underlying tinnitus generation: Results from PET and fMRI. *Hearing Research, 255*(1-2), 1-13. doi:10.1016/j.heares.2009.06.009

Le, T. N., Straatman, L. V., Lea, J., & Westerberg, B. (2017). Current insights in noise-induced hearing loss: A literature review of the underlying mechanism, pathophysiology, asymmetry, and management options. *Journal of Otolaryngology-Head & Neck Surgery, 46*, 41. doi:10.1186/s40463-017-0219-x

Leaver, A. M., Renier, L., Chevillet, M. A., Morgan, S., Kim, H. J., & Rauschecker, J. P. (2011). Dysregulation of limbic and auditory networks in tinnitus. *Neuron, 69*(1), 33-43. doi:10.1016/j.neuron.2010.12.002

Leckman, J. F., Sholomaskas, D., Thompson, W. D., Belanger, A., & Weissman, M. M. (1982). Best estimate of lifetime psychiatric-diagnosis - a methodological study. *Archives of General Psychiatry, 39*(8), 879-883.

Lee, M., Kim, S. E., Kim, W. S., Han, J., Kim, H. J., Kim, B. S., Kim, J. Y., Hong, S. B., Kim, B. G., & Lee, H. W. (2013). Cortico-cortical modulation induced by 1-hz repetitive transcranial magnetic stimulation of the temporal cortex. *Journal of Clinical Neurology, 9*(2), 75-82. doi:10.3988/jcn.2013.9.2.75

Lee, S. K., Chung, H., Chung, J. H., Yeo, S. G., Park, M. S., & Byun, J. Y. (2014). Effectiveness of transcutaneous electrical stimulation for chronic tinnitus. *Acta Oto-Laryngologica, 134*(2), 159-167. doi:10.3109/00016489.2013.844854

Lefaucheur, J. P., Andre-Obadia, N., Antal, A., Ayache, S. S., Baeken, C., Benninger, D. H., Cantello, R. M., Cincotta, M., de Carvalho, M., De Ridder, D., Devanne, H., Di Lazzaro, V., Filipovic, S. R., Hummel, F. C., Jaaskelainen, S. K., Kimiskidis, V. K., Koch, G., Langguth, B., Nyffeler, T., Oliviero, A., Padberg, F., Poulet, E., Rossi, S., Rossini, P. M., Rothwell, J. C., Schonfeldt-Lecuona, C., Siebner, H. R., Slotema, C. W., Stagg, C. J., Valls-Sole, J., Ziemann, U., Paulus, W., & Garcia-Larrea, L. (2014). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology, 125*(11), 2150-2206. doi:10.1016/j.clinph.2014.05.021 [doi]

Lefaucheur, J. (2012). Neurophysiology of cortical stimulation. *Emerging Horizons in Neuromodulation: New Frontiers in Brain and Spine Stimulation, 107*, 57-85. doi:10.1016/B978-0-12-404706-8.00005-X

Lefaucheur, J., Antal, A., Ayache, S. S., Benninger, D. H., Brunelin, J., Cogiamanian, F., Cotelli, M., De Ridder, D., Ferrucci, R., Langguth, B., Marangolo, P., Mylius, V., Nitsche, M. A., Padberg, F., Palm, U., Poulet, E., Priori, A., Rossi, S., Schecklmann, M., Vanneste, S., Ziemann, U., Garcia-Larrea, L., & Paulus, W. (2017). Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clinical Neurophysiology, 128*(1), 56-92. doi:10.1016/j.clinph.2016.10.087

Lehner, A., Schecklmann, M., Greenlee, M. W., Rupprecht, R., & Langguth, B. (2016). Triple-site rTMS

for the treatment of chronic tinnitus: A randomized controlled trial. *Scientific Reports, 6*, 22302. doi:10.1038/srep22302

Lehner, A., Schecklmann, M., Landgrebe, M., Kreuzer, P. M., Poeppl, T. B., Frank, E., Vielsmeier, V., Kleinjung, T., Rupprecht, R., & Langguth, B. (2012). Predictors for rTMS response in chronic tinnitus. *Frontiers in Systems Neuroscience, 6*, 11. doi:10.3389/fnsys.2012.00011

Lehner, A., Schecklmann, M., Poeppl, T. B., Kreuzer, P. M., Vielsmeier, V., Rupprecht, R., Landgrebe, M., & Langguth, B. (2013). Multisite rTMS for the treatment of chronic tinnitus: Stimulation of the cortical tinnitus network-A pilot study. *Brain Topography, 26*(3), 501-510. doi:10.1007/s10548-012-0268-4

Lehtimäki, J., Hyvarinen, P., Ylikoski, M., Bergholm, M., Makela, J. P., Aarnisalo, A., Pirvola, U., Makitie, A., & Ylikoski, J. (2013). Transcutaneous vagus nerve stimulation in tinnitus: A pilot study. *Acta Oto-Laryngologica, 133*(4), 378-382. doi:10.3109/00016489.2012.750736

Lenzenweger, M. F., Lane, M. C., Loranger, A. W., & Kessler, R. C. (2007). DSM-IV personality disorders in the national comorbidity survey replication. *Biological Psychiatry, 62*(6), 553-564. doi:10.1016/j.biopsych.2006.09.019

Levine, R. A., Abel, M., & Cheng, H. (2003). CNS somatosensory-auditory interactions elicit or modulate tinnitus. *Experimental Brain Research, 153*(4), 643-648. doi:10.1007/s00221-003-1747-3

Lin, J., & Staecker, H. (2006). Nonorganic hearing loss. *Seminars in Neurology, 26*(3), 321-330. doi:10.1055/s-2006-945518

Lobbestael, J., Leurgans, M., & Arntz, A. (2011). Inter-rater reliability of the structured clinical interview for DSM-IV axis I disorders (SCID I) and axis II disorders (SCID II). *Clinical Psychology & Psychotherapy, 18*(1), 75-79. doi:10.1002/cpp.693

Londero, A., Bonfils, P., & Lefaucheur, J. P. (2017). Transcranial magnetic stimulation and subjective tinnitus. A review of the literature, 2014-2016. *European Annals of Otorhinolaryngology, Head and Neck Diseases,* doi:10.1016/j.anorl.2017.12.001

Lopez-Gonzalez, M. A., & Esteban-Ortega, F. (2005). Tinnitus dopaminergic pathway. ear noises treatment by dopamine modulation. *Medical Hypotheses, 65*(2), 349-352. doi:10.1016/j.mehy.2005.02.016

Loranger, A. W., Sartorius, N., Andreoli, A., Berger, P., Buchheim, P., Channabasavanna, S. M., Coid, B., Dahl, A., Diekstra, R., Ferguson, B., Jacobsberg, L. B., Mombour, W., Pull, C., Ono, Y., & Regier, D. A. (1994). The international personality-disorder examination - the world-health-organization alcohol, drug-abuse, and mental-health administration international pilot-study of personality-disorders. *Archives of General Psychiatry, 51*(3), 215-224.

Malakouti, S., Mahmoudian, M., Alifattahi, N., & Salehi, M. (2011). Comorbidity of chronic tinnitus and mental disorders. *The International Tinnitus Journal, 16*(2), 118-122.

Marciano, E., Carrabba, L., Giannini, P., Sementina, C., Verde, P., Bruno, C., Di Pietro, G., & Ponsillo, N. G. (2003). Psychiatric comorbidity in a population of outpatients affected by tinnitus. *International Journal of Audiology, 42*(1), 4-9. doi:10.3109/14992020309056079

Marcondes, R. A., Sanchez, T. G., Kii, M. A., Ono, C. R., Buchpiguel, C. A., Langguth, B., & Marcolin, M. A. (2010). Repetitive transcranial magnetic stimulation improve tinnitus in normal hearing patients: A double-blind controlled, clinical and neuroimaging outcome study. *European Journal of Neurology, 17*(1), 38-44. doi:10.1111/j.1468-1331.2009.02730.x

Marriage, J., & Barnes, N. M. (1995). Is central hyperacusis a symptom of 5-hydroxytryptamine (5-ht) dysfunction. *Journal of Laryngology and Otology, 109*(10), 915-921.

Martikainen, I., Hagelberg, N., Jääskeläinen, S., Hietala, J., & Pertovaara, A. (2018). Dopaminergic and serotonergic mechanisms in the modulation of pain: In vivo studies in human brain. *European Journal of Pharmacology,* doi:10.1016/j.ejphar.2018.07.038

Martinez-Devesa, P., Perera, R., Theodoulou, M., & Waddell, A. (2010). Cognitive behavioural therapy for tinnitus. *Cochrane Database of Systematic Reviews,* (9), CD005233. doi:10.1002/14651858.CD005233.pub3

Martinez-Galan, J. R., Perez-Martinez, F. C., & Juiz, J. M. (2010). Differences in glutamate-mediated

calcium responses in the ventral cochlear nucleus and inferior colliculus of the developing rat. *Hearing Research, 267*(1-2), 46-53. doi:10.1016/j.heares.2010.03.089

Massimini, M., Ferrarelli, F., Esser, S. K., Riedner, B. A., Huber, R., Murphy, M., Peterson, M. J., & Tononi, G. (2007). Triggering sleep slow waves by transcranial magnetic stimulation. *Proceedings of the National Academy of Sciences of the United States of America, 104*(20), 8496-8501. doi:10.1073/pnas.0702495104

McCombe, A., Baguley, D., Coles, R., McKenna, L., McKinney, C., & Windle Taylor, P. (2001). Guidelines for the grading of tinnitus severity: The results of a working group commissioned by the british association of otolaryngologists, head and neck surgeons, 1999. *Clinical Otolaryngology & Allied Sciences, 26*(5), 388-393.

Mckee, G. J., & Stephens, S. (1992). An investigation of normally hearing subjects with tinnitus. *Audiology, 31*(6), 313-317.

Megwalu, U. C., Finnell, J. E., & Piccirillo, J. F. (2006). The effects of melatonin on tinnitus and sleep. *Otolaryngology-Head and Neck Surgery, 134*(2), 210-213. doi:10.1016/j.otohns.2005.10.007

Meikle, M., Stewart, B., Griest, S., & Henry, J. (2008). Tinnitus outcomes assessment. *Trends in Amplification, 12*(3), 223-235. doi:10.1177/1084713808319943

Mennemeier, M., Chelette, K. C., Allen, S., Bartel, T. B., Triggs, W., Kimbrell, T., Crew, J., Munn, T., Brown, G. J., & Dornhoffer, J. (2011). Variable changes in PET activity before and after rTMS treatment for tinnitus. *Laryngoscope, 121*(4), 815-822. doi:10.1002/lary.21425

Mielczarek, M., Konopka, W., & Olszewski, J. (2013). The application of direct current electrical stimulation of the ear and cervical spine kinesitherapy in tinnitus treatment. *Auris Nasus Larynx, 40*(1), 61-65. doi:10.1016/j.anl.2012.05.006

Mielczarek, M., Michalska, J., Polatynska, K., & Olszewski, J. (2016). An increase in alpha band frequency in resting state EEG after electrical stimulation of the ear in tinnitus patients - A pilot study. *Frontiers in Neuroscience, 10*, 453. doi:10.3389/fnins.2016.00453

Mielczarek, M., & Olszewski, J. (2014). Direct current stimulation of the ear in tinnitus treatment: A double-blind placebo-controlled study. *European Archives of Oto-Rhino-Laryngology, 271*(6), 1815-1822. doi:10.1007/s00405-013-2849-6

Moazami-Goudarzi, M., Michels, L., Weisz, N., & Jeanmonod, D. (2010). Temporo-insular enhancement of EEG low and high frequencies in patients with chronic tinnitus. QEEG study of chronic tinnitus patients. *Bmc Neuroscience, 11*, 40. doi:10.1186/1471-2202-11-40

Moerel, M., De Martino, F., & Formisano, E. (2014). An anatomical and functional topography of human auditory cortical areas. *Frontiers in Neuroscience, 8*, 225. doi:10.3389/fnins.2014.00225

Moisset, X., de Andrade, D. C., & Bouhassira, D. (2016). From pulses to pain relief: An update on the mechanisms of rTMS-induced analgesic effects. *European Journal of Pain, 20*(5), 689-700. doi:10.1002/ejp.811

Moller, A. R., & Rollins, P. R. (2002). The non-classical auditory pathways are involved in hearing in children but not in adults. *Neuroscience Letters, 319*(1), 41-44. doi:10.1016/S0304-3940(01)02516-2

Moller, A. R. (2011). In Moller, AR Langguth, B DeRidder, D Kleinjung,T. (Ed.), *Anatomy and physiology of the auditory system*. NEW YORK; 233 SPRING STREET, NEW YORK, NY 10013, UNITED STATES: SPRINGER. doi:10.1007/978-1-60761-145-5_8

Mora, R., Salami, A., Barbieri, M., Mora, F., Passali, G., Capobianco, S., & Magnan, J. (2003). The use of sodium enoxaparin in the treatment of tinnitus. *The International Tinnitus Journal, 9*(2), 109-111.

Muehlau, M., Rauschecker, J. P., Oestreicher, E., Gaser, C., Roettinger, M., Wohlschlaeger, A. M., Simon, F., Etgen, T., Conrad, B., & Sander, D. (2006). Structural brain changes in tinnitus. *Cerebral Cortex, 16*(9), 1283-1288. doi:10.1093/cercor/bhj070

Mueller, N., Lorenz, I., Langguth, B., & Weisz, N. (2013). rTMS induced tinnitus relief is related to an increase in auditory cortical alpha activity. *Plos One, 8*(2), e55557. doi:10.1371/journal.pone.0055557

Mulders, Wilhelmina H A M, Barry, K., & Robertson, D. (2014). Effects of furosemide on cochlear neural

activity, central hyperactivity and behavioural tinnitus after cochlear trauma in guinea pig. *PLoS One, 9*(5), e97948. doi:10.1371/journal.pone.0097948

Munchau, A., Bloem, B. R., Irlbacher, K., Trimble, M. R., & Rothwell, J. C. (2002). Functional connectivity of human premotor and motor cortex explored with repetitive transcranial magnetic stimulation. *Journal of Neuroscience, 22*(2), 554-561.

Newman, C. W., Jacobson, G. P., & Spitzer, J. B. (1996). Development of the tinnitus handicap inventory. *Archives of Otolaryngology-Head & Neck Surgery, 122*(2), 143-148.

Ngao, C. F., Tan, T. S., Narayanan, P., & Raman, R. (2014). The effectiveness of transmeatal low-power laser stimulation in treating tinnitus. *European Archives of Oto-Rhino-Laryngology, 271*(5), 975-980. doi:10.1007/s00405-013-2491-3

Ni, Z., Charab, S., Gunraj, C., Nelson, A. J., Udupa, K., Yeh, I., & Chen, R. (2011). Transcranial magnetic stimulation in different current directions activates separate cortical circuits. *Journal of Neurophysiology, 105*(2), 749-756. doi:10.1152/jn.00640.2010

Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *Journal of Physiology-London, 527*(3), 633-639. doi:10.1111/j.1469-7793.2000.t01-1-00633.x

Nitsche, M. A., & Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology, 57*(10), 1899-1901.

Noh, T., Kyong, J., Chang, M., Park, M., Lee, J., Oh, S., Kim, J., Chung, C., & Suh, M. (2017a). Comparison of treatment outcomes following either prefrontal cortical-only or dual-site repetitive transcranial magnetic stimulation in chronic tinnitus patients: A double-blind randomized study. *Otology & Neurotology, 38*(2), 296-303. doi:10.1097/MAO.0000000000001266

Noh, T., Rah, Y., Kyong, J., Kim, J., Park, M., Lee, J., Oh, S., Chung, C., & Suh, M. (2017b). Comparison of treatment outcomes between 10 and 20 EEG electrode location system-guided and neuronavigation-guided repetitive transcranial magnetic stimulation in chronic tinnitus patients and target localization in the asian brain. *Acta Oto-Laryngologica, 137*(9), 945-951. doi:10.1080/00016489.2017.1316870

Norena, A. J., & Eggermont, J. J. (2003). *Changes in spontaneous neural activity immediately after an acoustic trauma: Implications for neural correlates of tinnitus* doi://dx.doi.org.ezproxy.utu.fi/10.1016/S0378-5955(03)00225-9

Okabe, S., Hanajima, R., Ohnishi, T., Nishikawa, M., Imabayashi, E., Takano, H., Kawachi, T., Matsuda, H., Shiio, Y., Iwata, N. K., Furubayashi, T., Terao, Y., & Ugawa, Y. (2003). Functional connectivity revealed by single-photon emission computed tomography (SPECT) during repetitive transcranial magnetic stimulation (rTMS) of the motor cortex. *Clinical Neurophysiology, 114*(3), 450-457. doi:10.1016/S1388-2457(02)00408-X

Olver, J. S., O'Keefe, G., Jones, G. R., Burrows, G. D., Tochon-Danguy, H. J., Ackermann, U., Scott, A., & Norman, T. R. (2009). Dopamine D-1 receptor binding in the striatum of patients with obsessive-compulsive disorder. *Journal of Affective Disorders, 114*(1-3), 321-326. doi:10.1016/j.jad.2008.06.020

Ooms, E., Meganck, R., Vanheule, S., Vinck, B., Watelet, J., & Dhooge, I. (2011). Tinnitus severity and the relation to depressive symptoms: A critical study. *Otolaryngology-Head and Neck Surgery, 145*(2), 276-281. doi:10.1177/0194599811403381

Paaske, P. B., Kjems, G., Pedersen, C. B., & Sam, I. (1991). Zinc in the management of tinnitus - placebo-controlled trial. *Annals of Otology Rhinology and Laryngology, 100*(8), 647-649.

Park, S., Park, H., Kyeong, S., Moon, I. S., Kim, M., Kim, H. N., & Choi, J. (2013). Combined rTMS to the auditory cortex and prefrontal cortex for tinnitus control in patients with depression: A pilot study. *Acta Oto-Laryngologica, 133*(6), 600-606. doi:10.3109/00016489.2012.763181

Pattyn, T., Van den Eede, F., Vanneste, S., Cassiers, L., Veltman, D. J., Van de Heyning, P., & Sabbe, B. C. G. (2016). Tinnitus and anxiety disorders: A review. *Hearing Research, 333*, 255-265. doi:10.1016/j.heares.2015.08.014

Phillips, J. S., & McFerran, D. (2010). Tinnitus retraining therapy (TRT) for tinnitus. *Cochrane Database of Systematic Reviews,* (3), CD007330. doi:10.1002/14651858.CD007330.pub2

Piccirillo, J. F., Kallogjeri, D., Nicklaus, J., Wineland, A., Spitznagel, E. L.,Jr., Vlassenko, A. G., Benzinger, T., Mathews, J., & Garcia, K. S. (2013). Low-frequency repetitive transcranial magnetic stimulation to the temporoparietal junction for tinnitus four-week stimulation trial. *Jama Otolaryngology-Head & Neck Surgery, 139*(4), 388-395. doi:10.1001/jamaoto.2013.233

Picht, T., Schmidt, S., Brandt, S., Frey, D., Hannula, H., Neuvonen, T., Karhu, J., Vajkoczy, P., & Suess, O. (2011). Preoperative functional mapping for rolandic brain tumor surgery: Comparison of navigated transcranial magnetic stimulation to direct cortical stimulation. *Neurosurgery, 69*(3), 581-588. doi:10.1227/NEU.0b013e3182181b89

Pinto, P. C. L., Marcelos, C. M., Mezzasalma, M. A., Osterne, F. J. V., de Melo Tavares de Lima, M A, & Nardi, A. E. (2014). Tinnitus and its association with psychiatric disorders: Systematic review. *Journal of Laryngology and Otology, 128*(8), 660-664. doi:10.1017/S0022215114001030

Plewnia, C., Vonthein, R., Wasserka, B., Arfeller, C., Naumann, A., Schraven, S. P., & Plontke, S. K. (2012). Treatment of chronic tinnitus with theta burst stimulation A randomized controlled trial. *Neurology, 78*(21), 1628-1634.

Plewnia, C., Reimold, M., Najib, A., Brehm, B., Reischl, G., Plontke, S. K., & Gerloff, C. (2007). Dose-dependent attenuation of auditory phantom perception (tinnitus) by PET-guided repetitive transcranial magnetic stimulation. *Human Brain Mapping, 28*(3), 238-246. doi:10.1002/hbm.20270

Podoshin, L., Fradis, M., & Bendavid, Y. (1992). Treatment of tinnitus by intratympanic instillation of lignocaine (lidocaine) 2-per-cent through ventilation tubes. *Journal of Laryngology and Otology, 106*(7), 603-606. doi:10.1017/S0022215100120304

Polak, T., Markulin, F., Ehlis, A., Langer, J. B. M., Ringel, T. M., & Fallgatter, A. J. (2009). Far field potentials from brain stem after transcutaneous vagus nerve stimulation: Optimization of stimulation and recording parameters. *Journal of Neural Transmission, 116*(10), 1237-1242. doi:10.1007/s00702-009-0282-1

Poreisz, C., Boros, K., Antal, A., & Paulus, W. (2007). Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain Research Bulletin, 72*(4-6), 208-214. doi:10.1016/j.brainresbull.2007.01.004

Puel, J. L. (1995). Chemical synaptic transmission in the cochlea. *Progress in Neurobiology, 47*(6), +. doi:10.1016/0301-0082(95)00028-3

Puel, J. L., Ruel, J., Guitton, M., Wang, J., & Pujol, R. (2002). The inner hair cell synaptic complex: Physiology, pharmacology and new therapeutic strategies. *Audiology and Neuro-Otology, 7*(1), 49-54. doi:10.1159/000046864

Ramakers, G. G. J., Kraaijenga, V. J. C., Smulders, Y., van Zon, A., Stegeman, I., Stokroos, R., Free, R., Frijns, J. H. M., Huinck, W., Van Zanten, G., & Grolman, W. (2017). Tinnitus after simultaneous and sequential bilateral cochlear implantation. *Frontiers in Surgery, 4*, 65. doi:10.3389/fsurg.2017.00065

Raphael, Y., & Altschuler, R. A. (2003). Structure and innervation of the cochlea. *Brain Research Bulletin, 60*(5-6), 397-422. doi:10.1016/S0361-9230(03)00047-9

Rauschecker, J. P., Leaver, A. M., & Muehlau, M. (2010). Tuning out the noise: Limbic-auditory interactions in tinnitus. *Neuron, 66*(6), 819-826. doi:10.1016/j.neuron.2010.04.032

Rauschecker, J. P., May, E. S., Maudoux, A., & Ploner, M. (2015). Frontostriatal gating of tinnitus and chronic pain. *Trends in Cognitive Sciences, 19*(10), 567-578. doi:10.1016/j.tics.2015.08.002

Reich, J., Nduaguba, M., & Yates, W. (1988). Age and sex distribution of dsm-iii personality cluster traits in a community population. *Comprehensive Psychiatry, 29*(3), 298-303. doi:10.1016/0010-440X(88)90052-1

Rizzo, V., Siebner, H. R., Modugno, N., Pesenti, A., Munchau, A., Gerschlager, W., Webb, R. M., & Rothwell, J. C. (2004). Shaping the excitability of human motor cortex with premotor rTMS. *Journal of Physiology-London, 554*(2), 483-495. doi:10.1113/jphysiol.2003.048777

Roberts, L. E., Eggermont, J. J., Caspary, D. M., Shore, S. E., Melcher, J. R., & Kaltenbach, J. A. (2010).

Ringing ears: The neuroscience of tinnitus. *Journal of Neuroscience, 30*(45), 14972-14979. doi:10.1523/JNEUROSCI.4028-10.2010

Robins, L. N., Helzer, J. E., Croughan, J., & Ratcliff, K. S. (1981). "National-institute-of-mental-health diagnostic interview schedule - its history, characteristics, and validity. *Archives of General Psychiatry, 38*(4), 381-389.

Robins, L. N., Wing, J., Wittchen, H. U., Helzer, J. E., Babor, T. F., Burke, J., Farmer, A., Jablenski, A., Pickens, R., Regier, D. A., Sartorius, N., & Towle, L. H. (1988). The composite international diagnostic interview - an epidemiologic instrument suitable for use in conjunction with different diagnostic systems and in different cultures. *Archives of General Psychiatry, 45*(12), 1069-1077.

Robinson, S. K., Viirre, E. S., Bailey, K. A., Gerke, M. A., & Harris, J. P. (2005). Randomized placebo-controlled trial of a selective serotonin reuptake inhibitor in the treatment of nondepressed tinnitus subjects. *Psychosomatic Medicine, 67*(6), 981-988. doi:10.1097/01.psy.0000188479.04891.74

Roland, P., & Nergrd, C. (2012). [Ginkgo biloba--effect, adverse events and drug interaction]. *Tidsskrift for Den Norske Lgeforening, 132*(8), 956-959. doi:10.4045/tidsskr.11.0780

Rosenberg, S. I., Silverstein, H., Rowan, P. T., & Olds, M. J. (1998). Effect of melatonin on tinnitus. *Laryngoscope, 108*(3), 305-310. doi:10.1097/00005537-199803000-00001

Rossi, S., De Capua, A., Ulivelli, M., Bartalini, S., Falzarano, V., Filippone, G., & Passero, S. (2007). Effects of repetitive transcranial magnetic stimulation on chronic tinnitus: A randomised, crossover, double blind, placebo controlled study. *Journal of Neurology Neurosurgery and Psychiatry, 78*(8), 857-863. doi:10.1136/jnnp.2006.105007

Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., & Safety TMS Consensus Grp. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology, 120*(12), 2008-2039. doi:10.1016/j.clinph.2009.08.016

Roth, Y., Zangen, A., & Hallett, M. (2002). A coil design for transcranial magnetic stimulation of deep brain regions. *Journal of Clinical Neurophysiology, 19*(4), 361-370. doi:10.1097/00004691-200208000-00008

Ryan, D., & Bauer, C. A. (2016). Neuroscience of tinnitus. *Neuroimaging Clinics of North America, 26*(2), +. doi:10.1016/j.nic.2015.12.001

Sahlsten, H., Holm, A., Rauhala E., Takala, M., Löyttyniemi, E., Karukivi, M., Nikkilä, J., Ylitalo, K., Paavola, J., Johansson, R., Taiminen, T., & Jääskeläinen, S.K. (2019). Neuronavigated versus non-navigated repetitive transcranial magnetic stimulation for chronic tinnitus: A randomized study. *Trends in Hearing*, Jan;23:1-14. doi: 10.1177/2331216518822198

Sahlsten, H., Isohanni, J., Haapaniemi, J., Salonen, J., Paavola, J., Loyttyniemi, E., Johansson, R., & Jääskeläinen, S. K. (2015). Electric field navigated transcranial magnetic stimulation for chronic tinnitus: A pilot study. *International Journal of Audiology, 54*(12), 899-909. doi:10.3109/14992027.2015.1054041

Sahlsten, H., Taiminen, T., Karukivi, M., Sjösten, N., Nikkilä, J., Virtanen, J., Paavola, J., Joutsa, J., Niinivirta-Joutsa, K., Takala, M., Holm, A., Rauhala, E., Löyttyniemi, E., Johansson, R., & Jääskeläinen, S. K. (2018). Psychiatric (axis I) and personality (axis II) disorders and subjective psychiatric symptoms in chronic tinnitus. *International Journal of Audiology, 57*(4), 302-312. doi: 10.1080/14992027.2017.1409440

Sahlsten, H., Virtanen, J., Joutsa, J., Niinivirta-Joutsa, K., Löyttyniemi, E., Johansson, R., Paavola, J., Taiminen, T., Sjösten, N., Salonen, J., Holm, A., Rauhala, E., & Jääskeläinen, S. K. (2017). Electric field-navigated transcranial magnetic stimulation for chronic tinnitus: A randomized, placebo-controlled study. *International Journal of Audiology, 56*(9), 692-700. doi:10.1080/14992027.2017.1313461

Salihoglu, M., Ay, H., Cincik, H., Cekin, E., Cesmeci, E., Memis, A., Uzun, G., Altundag, A., & Simsek, K. (2015). Efficiency of hyperbaric oxygen and steroid therapy in treatment of hearing loss following acoustic trauma. *Undersea and Hyperbaric Medicine, 42*(6), 539-546.

Salonen, J., Johansson, R., & Joukamaa, M. (2007). Alexithymia, depression and tinnitus in elderly people.

General Hospital Psychiatry, 29(5), 431-435. doi:10.1016/j.genhosppsych.2007.05.002

Savage, J., & Waddell, A. (2014). Tinnitus. *Clinical Evidence, 2014*

Schaette, R., & McAlpine, D. (2011). Tinnitus with a normal audiogram: Physiological evidence for hidden hearing loss and computational model. *Journal of Neuroscience, 31*(38), 13452-13457. doi:10.1523/JNEUROSCI.2156-11.2011

Schecklmann, M., Vielsmeier, V., Steffens, T., Landgrebe, M., Langguth, B., & Kleinjung, T. (2012). Relationship between audiometric slope and tinnitus pitch in tinnitus patients: Insights into the mechanisms of tinnitus generation. *Plos One, 7*(4), e34878. doi:10.1371/journal.pone.0034878

Schlee, W., Hartmann, T., Langguth, B., & Weisz, N. (2009). Abnormal resting-state cortical coupling in chronic tinnitus. *Bmc Neuroscience, 10*, 11. doi:10.1186/1471-2202-10-11

Schlee, W., Weisz, N., Bertrand, O., Hartmann, T., & Elbert, T. (2008). Using auditory steady state responses to outline the functional connectivity in the tinnitus brain. *Plos One, 3*(11), e3720. doi:10.1371/journal.pone.0003720

Searchfield, G. D., Kaur, M., & Martin, W. H. (2010). Hearing aids as an adjunct to counseling: Tinnitus patients who choose amplification do better than those that don't. *International Journal of Audiology, 49*(8), 574-579. doi:10.3109/14992021003777267

Seidman, M. D., De Ridder, D., Elisevich, K., Bowyer, S. M., Darrat, I., Dria, J., Stach, B., Jiang, Q., Tepley, N., Ewing, J., Seidman, M., & Zhang, J. (2008). Direct electrical stimulation of heschl's gyrus for tinnitus treatment. *Laryngoscope, 118*(3), 491-500. doi:10.1097/MLG.0b013e31815daf5a

Seki, S., & Eggermont, J. J. (2003). *Changes in spontaneous firing rate and neural synchrony in cat primary auditory cortex after localized tone-induced hearing loss* doi://dx.doi.org.ezproxy.utu.fi/10.1016/S0378-5955(03)00074-1

Shargorodsky, J., Curhan, G. C., & Farwell, W. R. (2010). Prevalence and characteristics of tinnitus among US adults. *American Journal of Medicine, 123*(8), 711-718. doi:10.1016/j.amjmed.2010.02.015

Sharma, D. K., Kaur, S., Singh, J., & Kaur, I. (2012). Role of acamprosate in sensorineural tinnitus. *Indian Journal of Pharmacology, 44*(1), 93-96. doi:10.4103/0253-7613.91876

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., & Dunbar, G. C. (1998). The mini-international neuropsychiatric interview (MINI): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry, 59*, 22-33. doi:10.4088/JCP.09m05305whi

Shekhawat, G. S., Stinear, C. M., & Searchfield, G. D. (2013). Transcranial direct current stimulation intensity and duration effects on tinnitus suppression. *Neurorehabilitation and Neural Repair, 27*(2), 164-172. doi:10.1177/1545968312459908

Shi, Y., Burchiel, K. J., Anderson, V. C., & Martin, W. H. (2009). Deep brain stimulation effects in patients with tinnitus. *Otolaryngology-Head and Neck Surgery, 141*(2), 285-287. doi:10.1016/j.otohns.2009.05.020

Siebner, H. R., & Rothwell, J. (2003). Transcranial magnetic stimulation: New insights into representational cortical plasticity. *Experimental Brain Research, 148*(1), 1-16. doi:10.1007/s00221-002-1234-2

Siebner, H. R., Bergmann, T. O., Bestmann, S., Massimini, M., Johansen-Berg, H., Mochizuki, H., Bohning, D. E., Boorman, E. D., Groppa, S., Miniussi, C., Pascual-Leone, A., Huber, R., Taylor, P. C. J., Ilmoniemi, R. J., De Gennaro, L., Strafella, A. P., Kahkonen, S., Kloppel, S., Frisoni, G. B., George, M. S., Hallett, M., Brandt, S. A., Rushworth, M. F., Ziemann, U., Rothwell, J. C., Ward, N., Cohen, L. G., Baudewig, J., Paus, T., Ugawa, Y., & Rossini, P. M. (2009). Consensus paper: Combining transcranial stimulation with neuroimaging. *Brain Stimulation, 2*(2), 58-80. doi:10.1016/j.brs.2008.11.002

Simpson, R. B., Nedzelski, J. M., Barber, H. O., & Thomas, M. R. (1988). Psychiatric diagnoses in patients with psychogenic dizziness or severe tinnitus. *Journal of Otolaryngology, 17*(6), 325-330.

Slengerik-Hansen, J., & Ovesen, T. (2016). Botulinum toxin treatment of objective tinnitus because of essential palatal tremor: A systematic review. *Otology & Neurotology, 37*(7), 820-828. doi:10.1097/MAO.0000000000001090

Smallwood, R. F., Laird, A. R., Ramage, A. E., Parkinson, A. L., Lewis, J., Clauw, D. J., Williams, D. A., Schmidt-Wilcke, T., Farrell, M. J., Eickhoff, S. B., & Robin, D. A. (2013). Structural brain anomalies and chronic pain: A quantitative meta-analysis of gray matter volume. *Journal of Pain, 14*(7), 663-675. doi:10.1016/j.jpain.2013.03.001

Soleimani, R., Jalali, M. M., & Hasandokht, T. (2016). Therapeutic impact of repetitive transcranial magnetic stimulation (rTMS) on tinnitus: A systematic review and meta-analysis. *European Archives of Oto-Rhino-Laryngology, 273*(7), 1663-1675. doi:10.1007/s00405-015-3642-5

Sommer, M., Alfaro, A., Rummel, M., Speck, S., Lang, N., Tings, T., & Paulus, W. (2006). Half sine, monophasic and biphasic transcranial magnetic stimulation of the human motor cortex. *Clinical Neurophysiology, 117*(4), 838-844. doi:10.1016/j.clinph.2005.10.029

Speich, M., Pineau, A., & Ballereau, F. (2001). Minerals, trace elements and related biological variables in athletes and during physical activity. *Clinica Chimica Acta, 312*(1-2), 1-11. doi:10.1016/S0009-8981(01)00598-8

Steer, R. A., Ball, R., Ranieri, W. F., & Beck, A. T. (1999). Dimensions of the beck depression inventory-II in clinically depressed outpatients. *Journal of Clinical Psychology, 55*(1), 117-128. doi:AID-JCLP12>3.0.CO;2-A

Strafella, A. P., Paus, T., Barrett, J., & Dagher, A. (2001). Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. *Journal of Neuroscience, 21*(15), RC157.

Sukul, V. V., & Slavin, K. V. (2014). Deep brain and motor cortex stimulation. *Current Pain and Headache Reports, 18*(7), 427. doi:10.1007/s11916-014-0427-2

Sullivan, M. D., Katon, W., Dobie, R., Sakai, C., Russo, J., & Harropgriffiths, J. (1988). Disabling tinnitus - association with affective-disorder. *General Hospital Psychiatry, 10*(4), 285-291. doi:10.1016/0163-8343(88)90037-0

Sun, W., Lu, J., Stolzberg, D., Gray, L., Deng, A., Lobarinas, E., & Salvi, R. J. (2009). Salicylate increases the gain of the central auditory system. *Neuroscience, 159*(1), 325-334. doi:10.1016/j.neuroscience.2008.12.024

Sziklai, I., Szilvassy, J., & Szilvassy, Z. (2011). Tinnitus control by dopamine agonist pramipexole in presbycusis patients: A randomized, placebo-controlled, double-blind study. *Laryngoscope, 121*(4), 888-893. doi:10.1002/lary.21461

Taiminen, T., Kuusalo, L., Lehtinen, L., Forssell, H., Hagelberg, N., Tenovuo, O., Luutonen, S., Pertovaara, A., & Jääskeläinen, S. (2011). Psychiatric (axis I) and personality (axis II) disorders in patients with burning mouth syndrome or atypical facial pain. *Scand J Pain, 2*, 155-160.

Taiminen, T., Ranta, K., Karlsson, H., Lauerma, H., Leinonen, K. M., Wallenius, E., Kaljonen, A., & Salokangas, R. K. (2001). Comparison of clinical and best-estimate research DSM-IV diagnoses in a finnish sample of first-admission psychosis and severe affective disorder. *Nordic Journal of Psychiatry, 55*(2), 107-111. doi:10.1080/08039480151108507

Teismann, H., Wollbrink, A., Okamoto, H., Schlaug, G., Rudack, C., & Pantev, C. (2014). Combining transcranial direct current stimulation and tailor-made notched music training to decrease tinnitus-related distress - A pilot study. *Plos One, 9*(2), e89904. doi:10.1371/journal.pone.0089904

Theodoroff, S., Stevens, A., McMillan, G., Pettersson, D., Woodward, W., & Folmer, R. (2018). MRI verification of a 10-20 targeting protocol used during transcranial magnetic stimulation sessions for tinnitus. *Brain Topography,* doi:10.1007/s10548-018-0636-9

Thielscher, A., & Kammer, T. (2004). Electric field properties of two commercial figure-8 coils in TMS: Calculation of focality and efficiency. *Clinical Neurophysiology, 115*(7), 1697-1708. doi:10.1016/j.clinph.2004.02.019

To, W. T., De Ridder, D., Hart, J., Jr., & Vanneste, S. (2018). Changing brain networks through non-invasive neuromodulation. *Frontiers in Human Neuroscience, 12*, 128. doi:10.3389/fnhum.2018.00128

Topak, M., Sahin-Yilmaz, A., Ozdoganoglu, T., Yilmaz, H. B., Ozbay, M., & Kulekci, M. (2009). Intratympanic methylprednisolone injections for subjective tinnitus. *Journal of*

Laryngology and Otology, 123(11), 1221-1225. doi:10.1017/S0022215109990685

Torres, C. V., Moro, E., Lopez-Rios, A., Hodaie, M., Chen, R., Laxton, A. W., Hutchison, W. D., Dostrovsky, J. O., & Lozano, A. M. (2010). Deep brain stimulation of the ventral intermediate nucleus of the thalamus for tremor in patients with multiple sclerosis. *Neurosurgery, 67*(3), 646-651. doi:10.1227/01.NEU.0000375506.18902.3E

Trellakis, S., Lautermann, J., & Lehnerdt, G. (2007). Lidocaine: Neurobiological targets and effects on the auditory system. *Tinnitus: Pathophysiology and Treatment, 166*, 303-322. doi:10.1016/S0079-6123(07)66028-2

Tunkel, D. E., Bauer, C. A., Sun, G. H., Rosenfeld, R. M., Chandrasekhar, S. S., Cunningham, E. R. J., Archer, S. M., Blakley, B. W., Carter, J. M., Granieri, E. C., Henry, J. A., Hollingsworth, D., Khan, F. A., Mitchell, S., Monfared, A., Newman, C. W., Omole, F. S., Phillips, C. D., Robinson, S. K., Taw, M. B., Tyler, R. S., Waguespack, R., & Whamond, E. J. (2014). Clinical practice guideline: Tinnitus. *Otolaryngology--Head and Neck Surgery : Official Journal of American Academy of Otolaryngology-Head and Neck Surgery, 151*(2 Suppl), S40. doi:10.1177/0194599814545325

Turrigiano, G. G., & Nelson, S. B. (2004). Homeostatic plasticity in the developing nervous system. *Nature Reviews Neuroscience, 5*(2), 97-107. doi:10.1038/nrn1327

Tyler, R. S., & Baker, L. J. (1983). Difficulties experienced by tinnitus sufferers. *Journal of Speech and Hearing Disorders, 48*(2), 150-154. doi:10.1044/jshd.4802.150

Tyler, R., Cacace, A., Stocking, C., Tarver, B., Engineer, N., Martin, J., Deshpande, A., Stecker, N., Pereira, M., Kilgard, M., Burress, C., Pierce, D., Rennaker, R., & Vanneste, S. (2017). Vagus nerve stimulation paired with tones for the treatment of tinnitus: A prospective randomized double-blind controlled pilot study in humans. *Scientific Reports, 7*, 11960. doi:10.1038/s41598-017-12178-w

van den Berge, Minke J C, van Dijk, J Marc C, Free, R. H., Stienstra, J., van Dijk, P., & van der Laan, Bernard F A M. (2017). Effect of direct stimulation of the cochleovestibular nerve on tinnitus: A long-term follow-up study. *World Neurosurgery, 98*, 571-577. doi:10.1016/j.wneu.2016.11.036

van der Loo, E., Gais, S., Congedo, M., Vanneste, S., Plazier, M., Menovsky, T., Van de Heyning, P., & De Ridder, D. (2009). Tinnitus intensity dependent gamma oscillations of the contralateral auditory cortex. *Plos One, 4*(10), e7396. doi:10.1371/journal.pone.0007396

van Gendt, M. J., Boyen, K., de Kleine, E., Langers, D. R. M., & van Dijk, P. (2012). The relation between perception and brain activity in gaze-evoked tinnitus. *Journal of Neuroscience, 32*(49), 17528-17539. doi:10.1523/JNEUROSCI.2791-12.2012

Vanneste, S., & De Ridder, D. (2016). Deafferentation-based pathophysiological differences in phantom sound: Tinnitus with and without hearing loss. *NeuroImage, 129*, 80-94. doi:10.1016/j.neuroimage.2015.12.002

Viisanen, H., & Pertovaara, A. (2010). Roles of the rostroventromedial medulla and the spinal 5-HT1A receptor in descending antinociception induced by motor cortex stimulation in the neuropathic rat. *Neuroscience Letters, 476*(3), 133-137. doi:10.1016/j.neulet.2010.04.014

Weinmeister, K. P. (2000). Prolonged suppression of tinnitus after peripheral nerve block using bupivacaine and lidocaine. *Regional Anesthesia and Pain Medicine, 25*(1), 67-68. doi:10.1016/S1098-7339(00)80013-9

Weisz, N., Moratti, S., Meinzer, M., Dohrmann, K., & Elbert, T. (2005). Tinnitus perception and distress is related to abnormal spontaneous brain activity as measured by magnetoencephalography. *Plos Medicine, 2*(6), 546-553. doi:10.1371/journal.pmed.0020153

Weisz, N., Hartmann, T., Dohrmann, K., Schlee, W., & Norena, A. (2006). High-frequency tinnitus without hearing loss does not mean absence of deafferentation. *Hearing Research, 222*(1-2), 108-114. doi:10.1016/j.heares.2006.09.003

WHO Programme for the Prevention of Blindness and Deafness. (2006). *Primary ear and hearing*

care training resource Geneva : World Health Organization.

Wienbruch, C., Paul, I., Weisz, N., Elbert, T., & Roberts, L. E. (2006). Frequency organization of the 40-hz auditory steady-state response in normal hearing and in tinnitus. *NeuroImage, 33*(1), 180-194. doi:10.1016/j.neuroimage.2006.06.023

World Health Organization. (2016). International statistical classification of diseases and related health problems 10th revision. Retrieved from http://apps.who.int/classifications/icd10/browse/2016/en

Yamamoto, Y., Noguchi, Y., Enomoto, M., Yagishita, K., & Kitamura, K. (2016). Otological complications associated with hyperbaric oxygen therapy. *European Archives of Oto-Rhino-Laryngology, 273*(9), 2487-2493. doi:10.1007/s00405-015-3845-9

Ylikoski, J., Lehtimäki, J., Pirvola, U., Mäkitie, A., Aarnisalo, A., Hyvärinen, P., & Ylikoski, M. (2017). Non-invasive vagus nerve stimulation reduces sympathetic preponderance in patients with tinnitus. *Acta Oto-Laryngologica, 137*(4), 426-431. doi:10.1080/00016489.2016.1269197

Zald, D. H., Cowan, R. L., Riccardi, P., Baldwin, R. M., Ansari, M. S., Li, R., Shelby, E. S., Smith, C. E., McHugo, M., & Kessler, R. M. (2008). Midbrain dopamine receptor availability is inversely associated with novelty-seeking traits in humans. *Journal of Neuroscience, 28*(53), 14372-14378. doi:10.1523/JNEUROSCI.2423-08.2008

Zanarini, M. C., & Frankenburg, F. R. (2001). Attainment and maintenance of reliability of axis I and II disorders over the course of a longitudinal study. *Comprehensive Psychiatry, 42*(5), 369-374. doi:10.1053/comp.2001.24556

Zeman, F., Koller, M., Figueiredo, R., Aazevedo, A., Rates, M., Coelho, C., Kleinjung, T., de Ridder, D., Langguth, B., & Landgrebe, M. (2011). Tinnitus handicap inventory for evaluating treatment effects: Which changes are clinically relevant? *Otolaryngology-Head and Neck Surgery, 145*(2), 282-287. doi:10.1177/0194599811403882

Zenner, H., Delb, W., Kröner Herwig, B., Jäger, B., Peroz, I., Hesse, G., Mazurek, B., Goebel, G., Gerloff, C., Trollmann, R., Biesinger, E., Seidler, H., & Langguth, B. (2017). A multidisciplinary systematic review of the treatment for chronic idiopathic tinnitus. *European Archives of Oto-Rhino-Laryngology, 274*(5), 2079-2091. doi:10.1007/s00405-016-4401-y

Zenner, H., Vonthein, R., Zenner, B., Leuchtweis, R., Plontke, S. K., Torka, W., Pogge, S., & Birbaumer, N. (2013). Standardized tinnitus-specific individual cognitive-behavioral therapy: A controlled outcome study with 286 tinnitus patients. *Hearing Research, 298*, 117-125. doi:10.1016/j.heares.2012.11.013

Ziemann, U. (2004). TMS and drugs. *Clinical Neurophysiology, 115*(8), 1717-1729. doi:10.1016/j.clinph.2004.03.006

Zirke, N., Seydel, C., Arsoy, D., Klapp, B. F., Haupt, H., Szczepek, A. J., Olze, H., Goebel, G., & Mazurek, B. (2013). Analysis of mental disorders in tinnitus patients performed with composite international diagnostic interview. *Quality of Life Research, 22*(8), 2095-2104. doi:10.1007/s11136-012-0338-9

Zöger, S., Svedlund, J., & Holgers, K. M. (2001). Psychiatric disorders in tinnitus patients without severe hearing impairment: 24 month follow-up of patients at an audiological clinic. *Audiology, 40*(3), 133-140.

Zöger, S., Svedlund, J., & Holgers, K. M. (2006). Relationship between tinnitus severity and psychiatric disorders. *Psychosomatics, 47*(4), 282-288. doi:10.1176/appi.psy.47.4.282

Zrenner, C., Desideri, D., Belardinelli, P., & Ziemann, U. (2018). Real-time EEG-defined excitability states determine efficacy of TMS-induced plasticity in human motor cortex. *Brain Stimulation, 11*(2), 374-389. doi:10.1016/j.brs.2017.11.016

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