Towards a Moment of Silence:
Individualization of Acoustic Stimulation and Repetitive Transcranial Magnetic Stimulation in Tinnitus

Doctoral Thesis

in Fulfillment of the Requirements for the Doctoral Degree

in Human Sciences

(Dr. sc. hum.)

at the

Faculty of Medicine

at the University of Regensburg

submitted by

Stefan Schoisswohl

from

Linz, Austria

in the Year

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Der ist übel dran;
Denke, wer dich erst geführt,
Wer für dich getan!“

Johann Wolfgang von Goethe, 1749 – 1832, deutscher Dichter und Naturforscher

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Abstract

The continuous auditory perception of an acoustic stimulus without the existence of a corresponding source of sound is termed chronic subjective tinnitus and represents a relative common phenomenon in the global population. On the basis of varieties in phenotype and etiology, there is currently no effective treatment option or cure for tinnitus. Individualization of interventions represents a promising approach to cope with tinnitus heterogeneity. In the present thesis four separate experiments were conducted with a focus on transient changes in tinnitus perception and tinnitus-related electrophysiological brain activity caused either by acoustic stimulation or repetitive transcranial magnetic stimulation (rTMS). In study 1 different noise stimuli were modified according to patients' tinnitus characteristics and applied to noise-like and tonal tinnitus patients. Besides the ability of each stimulus in brief tinnitus suppression, superior loudness decreases were observed in noise-like tinnitus patients. The main goal of study 2 was to examine the consequences of different individualized sound stimuli on tinnitus-related electrophysiological brain activity and whether potential neural changes can be linked with tinnitus loudness alterations. Results indicate tinnitus-unspecific oscillatory brain activity changes due to sound stimulations plus an absence of behavioral and neural correlations. Contrasts between acoustic stimulation responders and non-responders showed enhanced alpha and diminished gamma band activity in the group of responders according to the current neural models for tinnitus. Additional analyses revealed post stimulation differences between these two subgroups especially in the alpha frequency band in auditory cortical regions. Study 3 and 4 are dedicated to rTMS single sessions in tinnitus. Study 3 was conceptualized as a technical feasibility report using a small sample of tinnitus patients with the aim to investigate the feasibility and reliability of rTMS individualization for tinnitus. Another objective was to ascertain if specific stimulation parameters provoke consistent tinnitus loudness changes. Different auditory cortex positions were stimulated with various frequencies over both hemispheres on two days. Findings indicate consistency of several stimulation parameters e.g., frequency for brief tinnitus suppression. Further, it was feasible to identify an individualized rTMS protocol for reliable placebo-superior tinnitus suppression in each patient. Insights from study 3 were transferred to succeeding study 4. The aim of study 4 was to systematically scrutinize the reliability of rTMS effects as well as the feasibility of rTMS individualization via single sessions using a bigger sample size and only one temporal cortex stimulation position. In addition to behavioral ratings, electrophysiological brain activity was recorded. No reliable rTMS-induced effects neither on tinnitus loudness nor oscillatory brain activity could be detected. Besides rTMS individualization based on behavioral responses, electrophysiological

data was used to identify a patient-specific rTMS protocol provoking changes in spontaneous brain activity according to neurophysiological models for tinnitus. RTMS individualization via behavioral and electrophysiological responses was feasible, but identification of an individualized protocol via electrophysiological responses seemed superior. The findings of the present thesis not only offer profound insights behind the basic and neurophysiological mechanisms of brief tinnitus suppression, but also provide useful indications and suggestions for prospective research attempts as well as treatment approaches in the fields of acoustic stimulation and rTMS for tinnitus.

Abstract (german)

Die kontinuierliche auditive Wahrnehmung eines akustischen Reizes in Abwesenheit einer entsprechenden Schallquelle wird als chronischer subjektiver Tinnitus bezeichnet und stellt ein global relativ häufig auftretendes Phänomen dar. Aufgrund vielfältiger Phänotypen und Ätiologien gibt es bis dato keine wirksamen Heilverfahren. Die Individualisierung von Interventionen bietet einen vielversprechenden Ansatz, um dieser Heterogenität entgegenzuwirken. Im Rahmen der vorliegenden Dissertation wurden insgesamt vier eigenständige Experimente zu akustischer Stimulation oder repetitiver transkranieller Magnetstimulation (rTMS) bei Tinnitus durchgeführt mit dem Ziel kurzzeitige Veränderungen der Tinnituswahrnehmung als auch elektrophysiologischer Hirnaktivität zu untersuchen. In Studie 1 wurden verschiedene rauschartige Stimuli gemäß den Tinnitus-Charakteristika von Patient*innen mit rauschhaftem oder tonalem Tinnitus modifiziert und für eine kurze akustische Stimulation verwendet. Eine temporäre Suppression des Tinnitus konnte bei allen applizierten Stimuli beobachtet werden. Patient*innen mit rauschhaftem Tinnitus zeigten jedoch eine deutlich stärkere Lautstärkeverminderung. Das Hauptziel von Studie 2 hingegen war es, die Auswirkungen von unterschiedlichen individualisierten rauschhaften Stimuli auf elektrophysiologische Hirnaktivität, assoziiert mit Tinnitus, zu überprüfen. Überdies ging Studie 2 der Frage nach, ob potenzielle neuronale Modulationen mit Veränderungen der Tinnituslautstärke in Zusammenhang stehen. Die Ergebnisse legten Tinnitus-unspezifische elektrophysiologische Veränderungen bedingt durch eine akustische Stimulation nahe, sowie keinen Zusammenhang von neuronalen und Verhaltensdaten. Patient*innen, die auf eine akustische Stimulation respondierten, zeigten erhöhte Alpha sowie verminderte Gamma Aktivität im Einklang mit den aktuellen neuronalen Modellen bei Tinnitus. Weitere Analysen brachten insbesondere Unterschiede im Alpha Frequenzband in auditorischen Bereichen des Kortex im Anschluss an eine Stimulation zum Vorschein. Studie 3 und 4 beschäftigten sich mit sogenannten rTMS Testsitzungen. Studie 3 wurde mit einer kleinen Stichprobe als eine technische Machbarkeitsstudie konzipiert. Das Ziel war es, die Machbarkeit und Zuverlässigkeit einer rTMS Individualisierung mittels Testsitzungen zu evaluieren. Ferner sollte herausgefunden werden, ob bestimmte Stimulationsparameter zuverlässige Veränderungen in der Tinnituslautstärke bewirken. Unterschiedliche Positionen des auditorischen Kortex wurden an zwei Tagen mit verschiedenen Frequenzen über beiden Hemisphären stimuliert. Bestimmte Stimulationsparameter wie etwa Frequenz, waren in der Lage konsistente Veränderungen in der Tinnituswahrnehmung hervorzurufen. Außerdem konnte für jede/n Patient*in ein individuelles rTMS Protokoll identifiziert werden, welches

zuverlässig die Tinnituslautstärke verringerte und dabei einer Placebostimulation überlegen war. Die gewonnen Erkenntnisse wurden zur Planung und Durchführung von Studie 4 genutzt. Studie 4 beabsichtigte neben der Reliabilitätsprüfung von rTMS Effekten auch die Möglichkeit der rTMS-Individualisierung anhand einer größeren Stichprobe und einer einzigen temporalen Stimulationsposition systematisch zu untersuchen. Zusätzlich zu Lautstärkebewertungen fanden elektroenzephalographische Aufzeichnungen statt. Es konnten weder reliable Veränderungen der Lautstärke noch reliable elektrophysiologische Hirnaktivitätsveränderungen bedingt durch rTMS nachgewiesen werden. Neben einer Individualisierung anhand von Verhaltensdaten wurden zudem elektrophysiologische Daten herangezogen. Das Ziel war die Identifizierung eines patientenspezifischen rTMS-Protokolls, welches neuronale Veränderungen entsprechend neurophysiologischer Modelle bei Tinnitus verursacht. Beide Individualisierungsansätze waren umsetzbar, wobei eine Individualisierung anhand von elektrophysiologischen Antworten überlegen zu sein scheint. Die vorliegenden Ergebnisse bieten nicht nur einen fundierten Einblick in die grundlegenden und neurophysiologischen Prozesse einer kurzzeitigen Unterdrückung der Tinnituswahrnehmung, sondern liefern auch nützliche Hinweise und Anregungen für zukünftige Forschungsarbeiten und Behandlungsansätze in den Bereichen akustische Stimulation und rTMS bei Tinnitus.

Glossary of terms

AM	Amplitude modulated
ANOVA	Analysis of Variance
aSTG	Anterior Superior Temporal Gyrus
BA	Brodmann Area
BDNF	Brain-derived Neurotrophic Factor
BP	Bandpass
CBT	Cognitive Behavioral Therapy
CR	Coordinated Reset
db	Decibel
EEG	Electroencephalography
ESIT-SQ	European School for Interdisciplinary Tinnitus Research - Screening Questionnaire
GUF	Questionnaire on Hypersensitivity to Sound
HL	Hearing Loss
Hz	Hertz
IBP	Individualized Bandpass Filter
IBS	Individualized Bandstop Filter
ICA	Independent Component Analysis
ITF	Individual Tinnitus Frequency
kHz	Kilohertz
LDL	Loudness Discomfort Level
LTD	Long-term Depression
LTP	Long-term Potentiation
MEG	Magnetoencephalography
MEP	Motor Evoked Potential

mini-HQ9	mini Hyperacusis Questionnaire
MML	Minimum Masking Level
MRI	Magnetic Resonance Imaging
MRIL	Minimum Residual Inhibition Level
mSTG	Middle Superior Temporal Gyrus
mtmfft	Multitaper Frequency Transformation
pSTG	Posterior Superior Temporal Gyrus
RI	Residual Inhibition
RMT	Resting Motor Threshold
rTMS	Repetitive Transcranial Magnetic Stimulation
SL	Sensation Level
SLIM	Synchronization-by-Loss-of-Inhibition-Model
SPL	Sound Pressure Level
TCD	Thalamo-cortical Dysrhythmia
THI	Tinnitus Handicap Inventory
TMNMT	Tailor-made Notched Music Training
TMS	Transcranial Magnetic Stimulation
TPJ	Temporo-parietal Junction
TQ	Tinnitus Questionnaire
TSCHQ	Tinnitus Sample Case History Questionnaire
V/m	Volt per Meter
VAS	Visual Analog Scale
WN	White Noise

1. Introduction

1.1. Tinnitus – definition, etiology, epidemiology and comorbidities

"*Tinnitus aurium*" (latin for ringing of the ears) or simply "*tinnitus*" describes the phenomenon of an auditory perception such as ringing, hissing or buzzing without the presence of any external source of sound. The sensation of this sound can be unilateral, bilateral but tinnitus can also be perceived within someone's head (Erlandsson and Dauman, 2013; Langguth et al., 2013; Roberts et al., 2010). Typically, tinnitus is classified as either subjective or objective. In the case of objective tinnitus an endogenous source of sound can be identified, which is perceptible by another person for instance an examiner (Hall et al., 2011). Objective tinnitus is rather rare (Tunkel et al., 2014) and can be caused for example by an abnormal blood flow or rhythmic muscle contractions (Langguth et al., 2013; Møller, 2007). If such an internal origin of sound does not exist and the sound is only perceived by the affected person, it is classified as subjective tinnitus (Baguley et al., 2013; Erlandsson and Dauman, 2013). A consistent perception of this auditory phantom sound for at least three (Hall et al., 2011) respectively six months (Mazurek et al., 2010) is considered as a chronification. Hereinafter, the term tinnitus is used synonymously for chronic subjective tinnitus. The most common causes for the development of tinnitus are cochlear damages towards noise trauma, presbyacusis or ototoxic medication (Langguth et al., 2013) and in particular hearing loss (Mazurek et al., 2010; Moore et al., 2017). In about 80% of cases, tinnitus is accompanied by some degree of hearing loss (Norena et al., 2002), whereby the frequency spectrum of maximum hearing loss usually overlaps with the perceived tinnitus pitch (Eggermont, 2007; Eggermont and Tass, 2015; Schecklmann et al., 2012).

With a prevalence of approximately 10 to 15%, tinnitus occurs relative frequently in the global population, whereas the elderly generation is particularly affected. Moreover, 2 - 3% of people concerned are significantly suffering from this phantom sound perception (Baguley et al., 2013; Hall et al., 2011; Heller, 2003; Langguth et al., 2019). In many cases tinnitus is accompanied by comorbidities such as depression (Salazar et al., 2019), anxiety disorders (Pattyn et al., 2016), sleep disorders (Croenlein et al., 2016), lowered quality of life (Nondahl et al., 2007; Weidt et al., 2016) or hyperacusis (Cederroth et al., 2020; Rosing et al., 2016; Schecklmann et al., 2014b) as well as altered auditory processing e.g., for speech perception (Jagoda et al., 2018) or sound source localization (Hyvärinen et al., 2016).

1.2. Pathophysiology

Originally tinnitus was considered as a solely disease of the inner ear. Though, after a surgical transection of the acoustic nerve, several tinnitus patients were still able to perceive the sound suggesting a substantial relevance of the central nervous system in the generation of tinnitus (House and Brackmann, 1981). Since that time extensive research in animal and human models has been performed, but yet the underlying pathophysiological mechanisms are not completely understood. In view of present research, peripheral as well as central mechanisms are similarly involved (Eggermont and Roberts, 2004; Elgoyhen et al., 2015; Jastreboff, 1990). As already mentioned, the dominant risk factor for tinnitus is hearing loss, whether it is due to noise trauma, permanent exposition to noisy environments or age-related (Ferreira et al., 2009; Møller, 2007; Nondahl et al., 2011; Shargorodsky et al., 2010). This assumption finds support in observations which report the tinnitus pitch frequency within the frequency spectrum of hearing loss (Basile et al., 2013; Norena et al., 2002; Schecklmann et al., 2012) or temporary tinnitus development in healthy subjects while wearing a silicone earplug (Schaette et al., 2012).

However, not every person with tinnitus shows hearing loss and vice versa (Norena et al., 2002; Roberts et al., 2008). The absence or the inability in detection of hearing deficits by audiometric methods (termed as hidden hearing loss), does not signify an absence of inner ear damages, cochlear damages respectively reduced peripheral auditory input (Kohrman et al., 2020; Schaette and McAlpine, 2011; Weisz et al., 2006).

The prevailing assumption about the generation of tinnitus suggests that due to damages of cochlear hair cells and the accompanying absent or diminished acoustic input from the periphery leads to a lack of neural input to auditory pathways and provokes maladaptive neuroplastic changes to auditory structures in the central nervous system which are suspected to be responsible for the phantom sound perception termed tinnitus (Eggermont, 2007; Eggermont and Roberts, 2012; Eggermont and Tass, 2015; Yang et al., 2011). Similar to other phantom percepts such as phantom pain after limb amputation (De Ridder et al., 2011), the brain tries to compensate for the deprivation of auditory information (De Ridder et al., 2014), unfortunately with false adjustment mechanisms as shortly explained below.

Neural alterations related to tinnitus are e.g., a dysbalance of inhibitory and excitatory spontaneous firing of deafferented neurons resulting in hyperactivity in auditory cortical structures (Noreña and Eggermont, 2006; Roberts et al., 2010; Shore et al., 2016) or abnormal neural synchrony and bursting along the auditory pathway (Noreña and Eggermont, 2006; Roberts et al., 2010). Further on, deafferentation could also manifest in a reorganization of the

tonotopic map of the auditory cortex. Thereby, neurons shift their characteristic frequency, which was initially within the frequency spectrum of hearing loss, to frequencies at the edge of hearing loss/ normal hearing. As a consequence frequencies at the edges are overrepresented in the tonotopic map (Eggermont and Roberts, 2004; Mühlnickel et al., 1998; Noreña and Eggermont, 2006; Roberts et al., 2010). According to Henry et al. (2014), these tonotopic map changes could also be responsible for aforementioned neural alterations related to tinnitus. However, the role of tonotopic map reorganization for the genesis of tinnitus is not clear (Eggermont and Roberts, 2012; Elgoyhen et al., 2015). Several neuroimaging studies were able to observe pathological hyperactivity in regions of the auditory cortex (Farhadi et al., 2010; Folmer, 2007; Langguth et al., 2006a; Weisz et al., 2007a) as well as tinnitus-related morphological mutations (Adjamian et al., 2014; Schecklmann et al., 2013b). This pathological changes are not only restricted to auditory areas, they are also observed in other, non-auditory regions of the brain (Adjamian et al., 2009, 2014; Lanting et al., 2009; Schlee et al., 2009a, 2014; Vanneste and De Ridder, 2012). For instance, Schlee et al. (2009) report tinnitus-related alterations in a widely spread network comprised of frontal, temporal as well as parieto-occipital cortical regions. Langguth et al. (2013) emphasize several neural networks such as the perceptual or salience network (conscious perception), the distress network (affective evaluation) or an engagement of memory mechanisms (persistent perception) involved in the perception of tinnitus, ultimately subsumed to a broad tinnitus brain network.
Due to the focus of the present thesis on electrophysiological measurements in tinnitus, tinnitus-related pathological ongoing brain activity is elucidated in more detail in the following section.

1.2.1. Pathological oscillatory brain activity in tinnitus

Tinnitus can even be associated with altered resting state brain activity patterns as measured in neurophysiological investigations by means of techniques like Electroencephalography (EEG) or Magnetoencephalography (MEG). These oscillatory aberrations were consolidated to the thalamo-cortical dysrhythmia model (TCD), which assumes the existence of a malfunctioning interaction between the thalamus and the cortex in tinnitus. According to the TCD model, peripheral deafferentation leads to spontaneous low frequency thalamic activity, which in turn results in a reduction of lateral inhibition in adjacent cortical areas causing tonotopic map reorganization as well as enhanced neural synchrony. Further, this translates into high frequency activity in auditory cortical areas, which is suspected to be relevant for the generation and maintenance of tinnitus (De Ridder et al., 2015b; Llinás et al., 2005, 1999).

Weisz et al. were able to identify deviations in tinnitus patients from healthy controls with respect to neuromagnetic spontaneous brain activity. In detail, increased delta and gamma activity plus reduced activity in the alpha frequency range over temporal regions were observed in individuals with tinnitus (Weisz et al., 2007b, 2005). Based upon these findings, the TCD model was further expanded to the "Synchronization-by-Loss-of-Inhibition-Model" (SLIM) (Weisz et al., 2007a). Upon the premise, that deafferentation leads to enhanced delta activity, the SLIM model claims that an additional suppression of inhibitory neurons leads to decreased alpha activity. Spontaneous activity in the alpha frequency band is considered as relevant for neural inhibitory processes (Klimesch et al., 2007; Weisz et al., 2011). In contrast to the TCD model, increased gamma activity occurs as a consequence of reduced inhibition respectively alpha activity, not as the product of an "edge effect". This pathological increased gamma activity was proposed to represent the oscillatory signature of tinnitus perception per se (Weisz et al., 2007b).

In accordance with the framework of the SLIM model, a decrease in alpha frequency band power along with an increase in gamma band activity was observed in tinnitus patients, whereby the power proportion of the frequency bands differed from a healthy control group (Lorenz et al., 2009). Further neurophysiological studies highlighted the relationship of enhanced delta and reduced alpha resting state brain activity with tinnitus perception as well as tinnitus distress (Adjamian et al., 2012; Balkenhol et al., 2013; Moazami-Goudarzi et al., 2010; Schlee et al., 2014). By means of neurofeedback training it was possible to substantiate the role of altered delta and alpha oscillatory brain activity in tinnitus. Only a simultaneous enhancement of alpha and reduction of delta frequency band activity was characterized by a lowering of tinnitus intensity, suggesting a strong reverse interplay of delta and alpha in tinnitus (Dohrmann et al., 2007). Tinnitus-specific activity in the gamma frequency range in auditory cortical areas (Ashton et al., 2007; S. Vanneste et al., 2011) as well as associations with tinnitus loudness (Balkenhol et al., 2013; van der Loo et al., 2009) underpin the relevance of gamma activity for tinnitus perception.

However, other studies were not able to demonstrate differences in alpha and delta band activity (Ashton et al., 2007) or rather differences in any frequency band (Zobay et al., 2015) between tinnitus patients and healthy controls nor connections of psychoacoustic or psychosocial measures of tinnitus with electrophysiological brain activity (Adjamian et al., 2012; Pierzycki et al., 2016). In contrast to the prevalent neural models for tinnitus, studies also demonstrated higher alpha activity in tinnitus patients as compared to a matched healthy control group

(Moazami-Goudarzi et al., 2010) or a positive correlation of alpha activity over the auditory cortex and tinnitus intensity (Meyer et al., 2014).
Additionally, the relevance of abnormal oscillatory brain activity in the theta and beta frequency range in tinnitus has been demonstrated (Balkenhol et al., 2013; Meyer et al., 2014; Moazami-Goudarzi et al., 2010). Recent work compared ongoing brain activity between subjects with sudden sensorineural hearing loss perceiving tinnitus and those without tinnitus and observed higher beta and gamma activity in frontal cortical regions (Lee et al., 2020).
Although extensive research has been carried out, discordant neurophysiological observations make a clear statement about pathological oscillatory brain activity associated with tinnitus rather difficult.

1.3. A cure for tinnitus?

Due to varieties in phenotype and etiology, the effects of currently available treatment approaches for tinnitus are only observed in a small number of patients – to date there is no effective treatment respectively cure for tinnitus (Hesse, 2016; Kleinjung and Langguth, 2020; Zenner et al., 2017). Several treatment approaches exist, these range from different sound therapies like noise generators, maskers or hearing aids (Hoare et al., 2014; Searchfield et al., 2017; Sereda et al., 2018) to cochlear implants (Peter et al., 2019; Ramakers et al., 2015), neurofeedback training (Güntensperger et al., 2017) and attempts in developing an appropriate drug therapy (Langguth et al., 2019) or the application of different non-invasive neuromodulation techniques (for an overview see Langguth, 2020). Tinnitus as a heterogenous condition with different causes and pathologies not fully understood yet, hampers the quest in finding a cure. Currently Cognitive Behavioral Therapy (CBT) is the prevailing treatment option with the best evidence by providing people appropriate coping strategies in order to deal with their tinnitus and therefore improving quality of life (Cima et al., 2012; Fuller et al., 2020). Personalization of treatments or individual treatment schedules might be a solution to account for tinnitus heterogeneity and variability in treatment effectiveness (Cederroth et al., 2019).
The personalization of treatment approaches is already deployed in multifactorial neuropsychiatric diseases such as depression (Cuijpers et al., 2012) or schizophrenia (Buckley and Miller, 2017). Due to various phenotypes in tinnitus it has already been suggested to neglect treatment effects on a whole group level and rather take individual results into account (Tyler et al., 2007).

1.4. Acoustic Stimulation

1.4.1. Sound therapy approaches

Potential treatment approaches for tinnitus are provided by research in the field of sound-based interventions. The administration of a sound simply to drown out someone's tinnitus tone is called tinnitus masking. The objective is to provide distraction or a short-term relief from the tinnitus by the application of more comfortable sounds (Hoare et al., 2014; Hobson et al., 2012). Tinnitus masking and even its combination with hearing aids were reported to improve tinnitus-related suffering (Aytac et al., 2017; Henry et al., 2015). In contrast to "classic" tinnitus masking, sound therapy approaches aim to use specific sounds to produce long-lasting clinical relevant changes in the tinnitus percept (Hoare et al., 2014; Hobson et al., 2012).

A joint application of low intensity sound stimulation alongside with counselling is termed Tinnitus Retraining Therapy and aims to modify pathological brain activity as well as to shift cognition about the tinnitus from negative to positive (Jastreboff, 2015). Various recent studies demonstrated positive effects of Tinnitus Retraining Therapy for the treatment of tinnitus (Barozzi et al., 2017; Bauer et al., 2017; Grewal et al., 2014). Likewise hearing aids (Sereda et al., 2018) and cochlear implants (Peters et al., 2016; Ramakers et al., 2015) are used for treatment and demonstrate positive effects. A further sound intervention is represented by a stimulation with notch-filtered music, thereby the individual tinnitus frequency (ITF) is removed from the music, which is then used for a long-term stimulation of several hours a day over a 12-month period of time. This personalized sound therapy is termed "tailor-made notched music training" (TMNMT) and is assumed to reverse maladaptive neuroplastic changes of the auditory cortex by an inhibition of neurons responding to frequencies within the notch-filter range referred to as lateral inhibition (Pantev et al., 2012). Some studies have assessed the efficacy of TMNMT and observed a reduction of tinnitus loudness and annoyance as well as a decrease in evoked neural activity associated with tinnitus (Okamoto et al., 2010; Stein et al., 2015; Wunderlich et al., 2015, 2015). Another form of sound therapy potentially reversing tinnitus-related neural pathologies is provided via acoustic coordinated reset (CR) neuromodulation (Tass et al., 2012; Tass and Popovych, 2012). Even though CR was reported as an effective treatment to reduce tinnitus-associated symptoms as well as to modulate tinnitus-related ongoing brain activity (Adamchic et al., 2017, 2014; Tass et al., 2012), a systematic review reports that given the studies available, there is not enough evidence for its clinical efficacy in tinnitus (Wegger et al., 2017). An extensive overview of potential sound therapy approaches deployed in tinnitus is provided by Searchfield et al. (2017) or Wang et al. (2020).

Furthermore, past basic research studies in the field of sound stimulation investigated different kinds of short-term sound stimulation techniques and were able to demonstrate a brief continuing suppression towards stimulation offset as described in the next paragraph.

1.4.2. Short-term acoustic tinnitus suppression – Residual Inhibition

Already in the 1970s and 1980s, Feldmann et al. investigated the possibility of short-term tinnitus suppression towards acoustic stimulation with pure tones, white noise and narrow-band noise. The authors observed a brief suppression of tinnitus perception towards a sound stimulation above the individual tinnitus loudness (Feldmann, 1983, 1971). This temporary tinnitus loudness suppression is designated as "residual inhibition" (RI).

RI is observed in approximately 60 – 80% of tinnitus cases with distinct suppression patterns per tinnitus patient, varying in depth, length and shape as a function of stimulation duration and intensity (Roberts et al., 2008; Terry et al., 1983; Vernon and Fenwick, 1984; Vernon and Meikle, 2003). To date several studies have investigated the effects of different sound stimulation techniques in RI. These range from an application of simple white noise (WN) or sine tones to the administration of particular filter techniques applied to these sound types (Henry et al., 2004, 2013; Neff et al., 2017, 2019b; Roberts et al., 2006, 2008). The effects of RI were demonstrated to be more effective with sounds close to or within the ITF spectrum (Roberts et al., 2008, 2006; Schaette et al., 2010; Sockalingam et al., 2007). A novel approach suggested by Fournier et al. (2018) not only highlights the relevance of stimulation frequency and intensity for RI induction, but also provides a fast and effective way of RI measurements. By an increasement of stimulation intensity of a customized narrowband noise until individuals' tinnitus was suppressed over the course of a silent period between stimulus presentation, the minimum residual inhibition level was defined (MRIL). With this method it was possible to induce RI in 86.7% of tinnitus patients.

Despite many research work in this field, up to now the fundamental neurophysiological mechanisms behind RI are not sufficiently understood (Roberts, 2007). Potential mechanisms of action are a momentary restoration of excitatory and inhibitory imbalances in auditory cortical areas or a desynchronization of tonotopic regions affected by hearing loss (Eggermont and Roberts, 2004; Roberts et al., 2008). Latest work from Galazyuk et al. suspects an attenuation of spontaneous firing neuron in the auditory system as the driving force behind short-term acoustic tinnitus suppression (Galazyuk et al., 2019, 2017).

Based on the results of previous described work on RI as well as the association of tinnitus with certain brain activity patterns, other studies went one step further and examined the effects of

different modulated sounds on temporary suppression of tinnitus. Sorts of amplitude modulated tones have been shown to entrain or modulate distinct oscillatory brain activity (Draganova et al., 2008; Picton et al., 2003). In order to hypothetically modify tinnitus-related spontaneous brain activity or rather alleviate hyperactivity in central auditory pathways, amplitude modulated tones near or at the ITF are utilized and indicate greater suppressing effects (Reavis et al., 2012, 2010; Tyler et al., 2014). Moreover, amplitude-modulated tones at the rate of the alpha frequency band with a carrier frequency of the individual tinnitus pitch were demonstrated to be superior in short-term tinnitus suppression than their unmodulated equivalents, tones with other carrier frequencies or other modulation rates (Neff et al., 2017, 2019b). Together these studies can not only provide basic insights behind the mechanisms of acoustic tinnitus suppression and tinnitus in general, in fact by investigation different kinds of filter or modulation techniques, the foundations for future potential sound therapies in tinnitus can be laid. However, in contrast to the large number of experiments focusing on the effects of several acoustic stimulation approaches on transient tinnitus loudness suppression, there is not much research on spontaneous brain activity patterns during RI.

1.4.3. Oscillatory brain activity during residual inhibition

Despite the importance of RI in understanding the mechanisms behind tinnitus, research examining oscillatory brain activity accompanying RI is rather scarce. Up to now only 5 studies focused on oscillatory brain activity during RI by means of EEG or MEG measurements. One of the first experiments in this field was conducted by Kristeva-Feige et al. (1995) and the usage of MEG recordings of spontaneous activity over the left auditory cortex during RI in a single tinnitus patient. During the periods where the patient was able to experience RI, an increase in low frequency spectral power (2 – 8 Hz) compared to periods without RI, was detected.

In another work, single subject intracranial recordings were used the scrutinize the neural correlates of RI. In contrast to the above-mentioned observation, a reduction in the delta (1 – 4 Hz) and theta (4 – 8 Hz) frequency bands during RI in auditory cortical regions was demonstrated. Further, an interaction of alpha (8 – 12 Hz), beta (20 – 28 Hz) and gamma (> 30 Hz) band activity with this reduced low-frequency activity was revealed (Sedley et al., 2015).

Sedley et al. (2012) were able to demonstrate positive correlations of power spectra in the delta (1.5 – 4 Hz), theta (4 – 8 Hz) and gamma (30 – 150 Hz) frequency range in auditory cortical regions with tinnitus intensity during RI by means of neuromagnetic measurements on a single subject level. The authors claim that these findings could be related to so-called higher states of tinnitus. Moreover, a negative correlation between gamma band activity and tinnitus

intensity during the state of residual excitation (transient tinnitus loudness increase), stresses the relevance of gamma for RI or rather for the perception of tinnitus per se (Sedley et al., 2012).

Essential work from Kahlbrock and Weisz (2008) likewise examined neuromagnetic spontaneous brain activity during RI. By defining RI as 50% tinnitus loudness reduction for at least 30 seconds towards stimulation offset, 10 out of 38 tinnitus patients exhibited RI. During short-term tinnitus loudness suppression, delta power (1.3 – 4 Hz) was decreased, while no changes in the gamma frequency (low: 30.5 – 49 Hz; high: 50.3 – 70.2 Hz) were present. The authors suggest that over the course of RI, pathological altered oscillatory brain activity patterns related to tinnitus might be briefly reversed, provoking a transient recovered balance of inhibitory and excitatory neural processes. In this case a reduction of tinnitus loudness is accompanied by a reduction of delta power (Kahlbrock and Weisz, 2008). A recent work examined the effects of a broad band noise stimulation on tinnitus loudness as well as spontaneous brain activity measured by EEG in 30 tinnitus patients. In 17 subjects it was feasible to induce RI. A comparison of electrophysiological brain activity during RI with a control condition and the absence of RI, demonstrated higher activity in the alpha and gamma frequency bands for the RI condition (King et al., 2020).

Taken together, the studies mentioned above were able to detect changes in oscillatory brain activity patterns during the state of transient tinnitus loudness suppression, but current observations are heterogeneous, limited by a lack of group-level analysis plus mixed methodological approaches and are only partial in accordance with the prevalent neurophysiological models for tinnitus.

1.5. Repetitive transcranial magnetic stimulation (rTMS)

1.5.1. Basic principles

Transcranial magnetic stimulation (TMS) represents a non-invasive brain stimulation method based on electromagnetic induction. Within certain guidelines, TMS is considered a safe and well tolerable neuromodulation technique (Lerner et al., 2019). By the application of brief electromagnetic pulses over the human head, electrical current transcends the cranial bone and depolarizes the underlying superficial neurons of the cortex perpendicular to the induced electrical current (Allen et al., 2007; Barker et al., 1985; Siebner et al., 2009). Extracerebral tissues (e.g., meninges) reduce the strength of the induced magnetic field (Klomjai et al., 2015),

therefore it is not possible to exceed a stimulation depth of maximum six centimeters (dependent on the type of stimulation coil) (Roth et al., 2007).

The rhythmic application of TMS pulses at a certain frequency is designated as repetitive transcranial magnetic stimulation (rTMS). Via rTMS it is feasible to induce neural consequences lasting longer than the actual stimulation period – induction of changes in neuroplasticity, (Hallett, 2007, 2000; Siebner and Rothwell, 2003). The induced neurophysiological effects strongly depend on the used rTMS parameters e.g., different stimulation protocols induce distinct changes in cortico-spinal excitability (Rossini et al., 2015). Low frequency protocols (≤ 1 Hz) are capable to evoke decreases, whereas with high frequency protocols (≥ 5 Hz) it is possible to induce increases in cortical excitability (Fitzgerald et al., 2006; Hoffman and Cavus, 2002; Pascual-Leone et al., 1994). However, these implications do not always apply and should therefore only be seen as rough guidelines (Fitzgerald, 2002; Fitzgerald et al., 2006; Klomjai et al., 2015; Rossini et al., 2015). Likewise the number of administered TMS pulses, the used stimulation intensity (Fitzgerald, 2002; Gamboa et al., 2010; Halawa et al., 2018; Nettekoven et al., 2014; Padberg et al., 2002) as well as the intrinsic state of the brain prior to stimulation (Siebner et al., 2004; Silvanto and Pascual-Leone, 2008; Weisz et al., 2012) might be relevant for the effect rTMS causes. Further research also highlights the significance of gene polymorphisms like the brain-derived neurotrophic factor (BDNF) as a predictor for respondence to non-invasive brain stimulation because of its connection to synaptic and cortical plasticity (Antal et al., 2010; Fidalgo et al., 2014; Polanía et al., 2018).

If rTMS is administered over several days or weeks, therapeutic effects take place conceivably caused via long-term potentiation (LTP) or long-term depression (LTD) of synaptic strength (Chervyakov et al., 2015; Hallett, 2000; Lefaucheur et al., 2014).

In the clinical context, rTMS is applied for a broad spectrum of psychiatric and neurologic disorders like schizophrenia, stroke, anxiety disorders or multiple sclerosis (Lefaucheur et al., 2020, 2014). With respect to guidelines for the clinical usage of rTMS, low frequency rTMS applied over the left temporo-parietal cortex may be effective for the treatment of tinnitus (Lefaucheur et al., 2020).

1.5.2. rTMS as a treatment approach for tinnitus

Tinnitus-associated pathological alterations of the central nervous system provide a substantial target for non-invasive brain stimulation techniques such as rTMS (Theodoroff and Folmer, 2013). Based on the premise, that low frequency rTMS is capable to provoke decreases in cortical excitability, this type of rTMS was used to counteract the dysbalance of inhibitory and

excitatory neural activity observed in tinnitus. In particular, 1 Hz rTMS over the left primary auditory cortex was utilized to diminish tinnitus-related overactivation of this brain region and potentially suppress individuals' tinnitus perception. In doing so, early studies were able to demonstrate an amelioration of tinnitus severity (Eichhammer et al., 2003; Langguth et al., 2003).

Since these early attempts, a vast amount of research was conducted to examine the efficacy of temporal rTMS for the treatment of tinnitus. Findings of subsequent studies are heterogeneous and, inter alia, characterized by a high inter-individual variability in rTMS responses (Schoisswohl et al., 2019a). This lack of clarity is further exemplified by two placebo-controlled, randomized clinical trials deploying the current prevalent rTMS treatment approach applied in tinnitus – 1 Hz rTMS over the temporal cortex on 10 days à 2000 pulses per session. Findings from Folmer et al. (2015) demonstrate an improvement in tinnitus severity by means of a higher number of stimulation responders for verum rTMS in contrast to a placebo stimulation condition. Improvements also continued over the follow-up period for the subgroup of responders. These findings are countered by the results of a multi-centre trial from Landgrebe et al. (2017). The authors could not observe a therapeutic advantage of verum rTMS in contrast to a placebo stimulation, neither directly after the end of the intervention nor during the follow-up period.

In light of this uncertainty about effectiveness of temporal rTMS together with the assumption that pathological alterations in tinnitus do not only occur in auditory regions, rather a network comprised of auditory and non-auditory brain regions is involved, other trials went one step further and examined the effectiveness of prefrontal (De Ridder et al., 2013; Sven Vanneste et al., 2011b) as well as a combination of prefrontal and temporal magnetic stimulations (Kleinjung et al., 2008; Kreuzer et al., 2011; Lehner et al., 2013; Noh et al., 2020, 2017).

In a randomized clinical trial by Lehner et al. (2016), tinnitus patients were simultaneously stimulated over the left dorsolateral prefrontal cortex and bilaterally over the temporo-parietal cortex. Although, so-called triple-site rTMS was able to reduce tinnitus severity, no statistical superiority compared to a stimulation of the left temporal cortex (single-site) could be demonstrated.

Other trials scrutinized the effectiveness of high frequency protocols (Forogh et al., 2014; Khedr et al., 2010, 2008), high frequency priming stimulations of the temporal cortex prior low frequency rTMS (Langguth et al., 2008), continuous theta-burst stimulations (Chung et al., 2012; Plewnia et al., 2012; Schecklmann et al., 2016) as well as the combination of rTMS with certain types of psychotropic medications (Bilici et al., 2015; Kleinjung et al., 2011, 2009).

Alternative approaches even combined rTMS with peripheral muscle stimulations (Vielsmeier et al., 2018), low level laser therapy (Thabit et al., 2015) or relaxation techniques (Kreuzer et al., 2016).

Despite the great number of research in this field, the clinical effectiveness of rTMS is still not clear yet as indicated by recent reviews and meta-analysis (Dong et al., 2020; Langguth, 2020; Zenner et al., 2017). In contrast, others report medium to large effect sizes (Soleimani et al., 2016) or even potential effectiveness for its application over auditory cortical areas (Lefebvre-Demers et al., 2020). Potential explanations for this variability in the effectiveness might not only derive from inter-individual responses to rTMS, but also from a lack of clarity about appropriate stimulation parameters for the application in tinnitus. A promising concept to account for this uncertainty and enhance the efficacy of rTMS as a treatment option was presented by Kreuzer et al. (2017) via an individualization of rTMS protocols using single sessions.

The feasibility to transient suppress or diminish the perception of tinnitus with rTMS single sessions and only a small number of administered pulses has already been demonstrated by several experiments (Folmer et al., 2006; Lorenz et al., 2010; Meeus et al., 2009).

Kreuzer et al. (2017) stimulated 25 tinnitus patients with different rTMS protocols over prefrontal and temporo-parietal cortical regions during single sessions prior to an actual treatment. The attempt was to identify the most effective rTMS protocol for brief tinnitus loudness suppression per patient. In case of a response, the detected protocol was used for a daily treatment. If such a protocol was not identifiable, patients were treated with a standard protocol (left frontal 20 Hz followed by left temporal 1 Hz rTMS). In nearly half of the patients investigated an individualized rTMS protocol was identified. Further, a higher number of treatment responders in the group which received their individualized rTMS protocol could be demonstrated.

These observations not only highlight the feasibility to customize rTMS for tinnitus by means of single sessions but could also provide a way to overcome the variability of effects observed in rTMS trials. Similar to research in the field of RI, additional studies took the next step and combined single session rTMS with measurements of spontaneous brain activity.

1.5.3. rTMS effects on tinnitus-related oscillatory brain activity

As already outlined in the pathophysiology section of the present thesis, there is no explicit neurophysiological marker for tinnitus. A combination of TMS with EEG or MEG recordings might have the potential to shed light on this discussion. It is now well established from a variety

of experiments, that rTMS is capable to generate changes in evoked brain activity as well as to produce neuroplastic consequences measured on the basis of oscillatory brain activity alterations. (Lorenz et al., 2010; Noda, 2020; Qiu et al., 2019; Saari et al., 2018; Thut and Pascual-Leone, 2010; Van Doren et al., 2015; Woźniak-Kwaśniewska et al., 2014).

For example, TMS in the alpha frequency range is reported to induce oscillatory activity in the alpha band (Thut et al., 2011) or long lasting consequences in ongoing brain activity due to TMS were observed (Ding et al., 2014). TMS-EEG approaches are used in the clinical context as well. The aim is to identify potential biomarker, gain deeper insights in the pathophysiology as well as to uncover TMS-related neuroplastic alterations in certain types of neuropsychiatric diseases (Hui et al., 2019; Tremblay et al., 2019). In the context of tinnitus a comparison of neurophysiological activity before and after rTMS treatments revealed enhanced power in the alpha frequency range (Noh et al., 2019) in accordance to the SLIM model as well as decreased evoked activity alongside with tinnitus severity reduction (L. P.-H. Li et al., 2019).

In addition to the well-known possibility to temporary suppress the tinnitus percept with single rTMS sessions, up to now two studies investigated the neurophysiological consequences of short magnetic stimulations in tinnitus and demonstrated the possibility to modulate tinnitus-related spontaneous brain activity patterns. By the application of different types of rTMS protocols over the temporal cortex, Müller et al. (2013) found a significant increase of alpha band power (8 – 12 Hz) in the auditory cortex associated with strong reductions in reported tinnitus loudness. Interestingly, the authors also observed unspecific left frontal reductions of alpha and high gamma (70 – 90 Hz) band activity, which were related to increases in loudness ratings. Equally by means of single rTMS sessions and 1 Hz stimulations with 200 pulses over several positions (frontal, temporal, parietal) in tinnitus patients and healthy controls, Schecklmann et al. (2015) demonstrated decreases in the beta3 (21.5 – 30 Hz) and gamma (30.5 – 44 Hz) frequency band power over temporal areas after a right frontal stimulation in tinnitus patients. Left temporal low frequency rTMS reduced band power in the delta (2 – 3.5 Hz) and theta (4 – 7.5 Hz) frequency ranges, while beta2 (18.5 – 21 Hz) band power was enhanced. However, no statistical relevant changes in tinnitus loudness were observed.

Observations made by the above-mentioned single sessions experiments match the neurophysiological models for tinnitus established by EEG and MEG research. The combination of TMS-EEG in single rTMS sessions provides essential fundamental research in order to detect the oscillatory signature of short-term tinnitus loudness reductions and not only improves our understanding of neuroplastic consequences of rTMS but also provides insights in the pathological altered brain activity patterns underlying the tinnitus percept.

2. Scope and objective of the present doctoral thesis

In the present thesis four separate yet topically interconnected experiments were conducted. All four studies were executed at the Centre for Neuromodulation of the University of Regensburg. The overarching objective was to gain more profound insights behind the mechanisms of short-term tinnitus loudness suppression by means of short acoustic stimulation techniques (**study 1** and **study 2**) and short rTMS test sessions (**study 3** and **study 4**). Each study represents an independent research work submitted to or already published in relevant peer-reviewed journals. **Study 1** and **study 3** are already published in suitable journals. Submitted manuscripts were additionally posted on the preprint servers bioRχiv or medRχiv. The text, tables and figures used are pre-copy-edited versions of the manuscripts submitted/ published. Figures and tables are numbered chronologically and placed in the text for the sake of readability.

Study 1 aimed at systematically investigate the effects of several personalized noise stimulations to establish novel and more profound sound stimulation techniques for brief tinnitus suppression in tonal and in particular noise-like tinnitus. Besides the application of different amplitude modulation rates to white noise, stimuli were personalized according to participants' tinnitus characteristics. For this purpose, stimuli were adjusted with respect to patients' individual tinnitus loudness as well as filtered according to patients' individual tinnitus pitch respectively noise-band characteristics. Further, these two techniques were deployed simultaneously in a novel combinatory approach.

In the same vein, **study 2** examined the effects of various personalized noise stimulation techniques on RI. However, the main goal of this experiment was to investigate the consequences of different noise stimuli types on tinnitus-related oscillatory brain activity measured via EEG and whether potential EEG changes can be associated with subjective tinnitus loudness alterations. Additionally, EEG activity between acoustic stimulation responder and non-responder was compared in order to assess if a transient suppression of the tinnitus percept is reflected by a temporal reversion of tinnitus-associated pathological brain activity as suggested by previous work. Findings and insight from this study might not only be useful to understand the neural mechanisms behind RI but also tinnitus in general.

A potential way to overcome the variability of rTMS effects as well as the uncertainty about appropriate stimulation parameters in tinnitus might be the identification of a patient-specific rTMS protocol for short-term tinnitus suppression by means of rTMS test sessions. Such an rTMS individualization is reported to be a feasible and promising approach by means of a preceding study. **Study 3** and **study 4** of the present thesis intended to focus on the

individualization of rTMS via single rTMS sessions in more detail. **Study 3** was conceptualized as a technical feasibility study with a sample of 5 tinnitus patients. RTMS was administered during single sessions on two days over different positions of the temporal cortex with various frequencies using a novel e-field guided neuronavigation system. The objective was to evaluate feasibility and reliability of an rTMS individualization as well as if certain stimulation parameters produce consistent changes in tinnitus loudness. Building up on the insights gained from **study 3**, the purpose of subsequent **study 4** was to scrutinize rTMS individualization as well as test-retest reliability of rTMS-induced tinnitus loudness changes in-depth using a bigger sample size. Moreover, concurrent EEG measurements of patients' brain activity, enabled an evaluation of test-retest reliability regarding rTMS-induced changes in oscillatory bran activity. Beyond the individualization of rTMS by behavioral ratings of tinnitus loudness changes, a novel attempt was undertaken to individualize rTMS based on electrophysiological responses according to the current prevalent neurophysiological models in tinnitus.

3. Study 1 – Amplitude Modulated Noise for Tinnitus Suppression in Tonal and Noise-Like Tinnitus

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Abstract

Background: The phenomenon of short-term tinnitus suppression by different forms of acoustic stimulation is referred to as residual inhibition (RI). RI can be triggered in the majority of tinnitus cases and was found to be depending on the used intensity, length or types of sounds. Past research already stressed the impact of noise stimulation as well as the superiority of amplitude modulated (AM) pure tones at the individual tinnitus frequency for RI in tonal tinnitus. Recently a novel approach for the determination of noise-like tinnitus characteristics was proposed. **Objectives:** The aim of the present study was to investigate whether in participants with noise-like tinnitus RI can be increased by AM noise stimuli according to the individual tinnitus frequency range. **Methods:** For this purpose the individual tinnitus characteristics (noise-like and tonal tinnitus) of 29 people affected by tinnitus (mean age = 55.59, 7 females, mean tinnitus duration = 159.97 months) were assessed via customizable noise- band matching. The objective was to generate bandpass filtered stimuli according to the individual tinnitus sound (individualized bandpass filtered (IBP) sounds). Subsequently, various stimuli differing in bandpass filtering and AM were tested with respect to their potential to induce RI. Participants were acoustically stimulated with 7 different types of stimuli for 3 min each and had to rate the loudness of their tinnitus after each stimuli. **Results:** Results indicate a general efficacy of noise stimuli for the temporary suppression of tinnitus, but no significant differences between AM and unmodulated IBP. Significantly better effects were observed for the subgroup with noise-like tinnitus (n = 14), especially directly after stimulation offset. **Conclusion:** The study at hand provides further insights in potential mechanisms behind RI for different types of tinnitus. Beyond that, derived principles may qualify for new or extend current tinnitus sound therapies.

Introduction

Chronic subjective tinnitus is defined as the permanent perception of a sound such as ringing or hissing in the absence of an external or internal source of noise. Approximately 10 – 15% of the population in industrial countries experience this phantom sound (Erlandsson and Dauman, 2013; Hall et al., 2011; Heller, 2003; Langguth et al., 2013). Causes for the development of tinnitus are divergent and not completely understood, though most commonly tinnitus occurs towards cochlear damages due to noise trauma (Langguth et al., 2013). In the majority of cases, the perceived tinnitus pitch is in accordance with the frequency spectrum of hearing loss (HL) (Basile et al., 2013; Roberts et al., 2008). As a consequence of decreased or absent auditory input and the subsequent deficiency of neural input, maladaptive pathological changes in the auditory pathway are formed, which lead to the perception of a "phantom sound" defined as tinnitus (Eggermont, 2007; Eggermont and Roberts, 2012; Eggermont and Tass, 2015). Neurophysiological investigations of tinnitus were able to demonstrate hyperactivity in auditory brain areas (Farhadi et al., 2010; Folmer, 2007) as well as aberrant oscillatory brain activity and connectivity patterns (Moazami-Goudarzi et al., 2010; Mohan et al., 2016; Schlee et al., 2009a, 2014). Available treatment options have only limited efficacy and to date there is no cure available (Baguley et al., 2013).

Auditory stimulation is one potential treatment approach for tinnitus, but also provides insights to basic mechanisms of tinnitus (Fournier et al., 2018; Roberts et al., 2008). Almost half a century ago, Feldmann (Feldmann, 1983, 1971) investigated the phenomenon of short-term tinnitus suppression after sound stimulation. This temporary suppression is referred to as "residual inhibition" (RI), which manifests in individual suppression patterns (i.e., duration, depth and shape) and can be triggered in 60 – 80% of tinnitus cases (Roberts, 2007; Vernon and Meikle, 2003). Various recent studies scrutinized RI in more depth. Data from several investigations suggest the effects of RI to be more prominent with sounds close or within the individual tinnitus frequency spectrum (Roberts et al., 2006; Schaette et al., 2010). Factors including duration or intensity of the stimuli also affect RI (Neff et al., 2017; Norena et al., 2002; Terry et al., 1983; Vernon and Fenwick, 1984).

In contrast, the underlying neurophysiological mechanisms of RI are not clearly understood yet (Galazyuk et al., 2019; Roberts, 2007). Most recent work suggests that tinnitus suppression through sound stimulation is related to reduced spontaneous firing of central auditory neurons (Galazyuk et al., 2019, 2017). The importance of stimulation intensity and frequency was verified in a recent work from Fournier et al. (Fournier et al., 2018), who developed a novel approach for RI testing described as Minimum RI Level. Thereby, people had to adjust the

intensity of customized stimuli up to the point where their tinnitus is suppressed during a given interval after the offset of the stimulus. Results show an occurrence of RI in 86.7% of people with tinnitus by using this method (Fournier et al., 2018). Despite noise-like tinnitus perception in many cases, to the best of our knowledge, none of the previous mentioned studies included a genuine matching for noise-like tinnitus, that is, determination of noise band-width (Fournier et al., 2018; Roberts et al., 2006). Recently Henry et al. (2013) proposed a novel approach for tinnitus matching procedures taking into consideration the tinnitus type. In addition to the determination of the centre frequency, people with tinnitus were also able to adjust the band-width of their tinnitus (Henry et al., 2013).

Here we aim to use both frequency and band-with information to develop individualized stimuli, especially for people with noise-like tinnitus, for the investigation of RI. Previous studies investigating the effects of differently modulated sounds on RI revealed that amplitude modulated (AM) tones near or at the individual tinnitus frequency result in larger RI (Reavis et al., 2012; Tyler et al., 2014). Furthermore, differential results for specific amplitude modulation rates were observed (Neff et al., 2017, 2019b). The experiment aims at investigating the effects of different noise stimuli with and without AM on RI. The overarching goal is to establish new acoustic stimulation techniques for basic RI research as well as generating principles for possible future sound stimulation concepts with the AM stimulus class. For this purpose, the individual tinnitus characteristics are assessed via noise-band matching as suggested by Henry et al. (2013) in order to create personalized stimuli for RI examination.

Previous studies in the field of RI already emphasized the impact of noise stimulation on tinnitus perception in tonal tinnitus (Fournier et al., 2018; Henry et al., 2013; Roberts et al., 2008, 2006). To the best of our knowledge, none of the existing experiments systematically investigated these noise stimulation methods, in particular the application of AM or bandpass filters (BP) to noise stimuli, in noise-like tinnitus. According to this, the current experiment represents the first attempt to investigate the effects of an administration of individualized BP settings (IBP) and different rates of AM (10 and 40 Hz) to white noise (WN) on RI. These stimulation methods are furthermore merged to a novel combinatory approach to apply IBP and AM to WN simultaneously and scrutinize its efficacy in RI. Additionally, each of the used stimuli was examined with regards to induced arousal and valence as rated by the participants, since differences in stimuli evaluation could potentially affect tinnitus suppression. Besides the assumption of the efficacy of all deployed noise stimuli in short-term tinnitus inhibition (in both noise-like and tonal tinnitus), we expect that IBP differs in its effects on RI from unadjusted WN. We hypothesized that the IBP would result in different strengths of residual tinnitus

suppression compared to WN. Yet, given the lack of previous studies we are not able to define a directed hypothesis here. Furthermore, building on the insights of previous work, we hypothesize that stimulations with AM noise (filtered or unchanged) result in larger RI than their unmodulated counterparts.

Methods

Participants

The sample for this experiment consisted of 29 participants (7 female) between 18 and 75 years with noise-like (n = 14) or tonal tinnitus (n = 15) with a tinnitus duration of > 6 months. Participants were recruited from the Interdisciplinary Tinnitus Centre in Regensburg, Germany. For detailed sample characteristics see **Table 1**. Primary inclusion criteria were no somatic, mental health or neurological conditions and no current intake of psychotropic medications or substances. Alike, participants were not allowed to participate in other tinnitus-related studies. The methods and the procedures used in this study were examined and approved by the local Ethics Committee of the University of Regensburg (16-101-0061). All participants were sufficiently informed about the aim, methods, and duration of the study, possible side effects, and gave written informed consent prior to the start of the experiment.

Psychometry

Each participant filled in an online survey composed of German versions of the Tinnitus Handicap Inventory (Kleinjung et al., 2007a; Newman et al., 1996), the Tinnitus Questionnaire (TQ) (Goebel and Hiller, 1994; Hallam et al., 1988), a brief version of the Hyperacusis Questionnaire (mini-HQ9) (Goebel et al., 2013) and the Tinnitus Sample Case History Questionnaire for tinnitus-related clinical and demographic information (Langguth et al., 2007).

Audiometry

For the purpose of individual hearing threshold determination, frequencies ranging from 125 Hz to 8kHz in octave steps including semi-octave steps between 0.5 and 1 (i.e., 0.75 kHz), 1 and 2 (i.e., 1.5 kHz), 2 and 4 (i.e., 3 kHz) and 4 and 8 kHz (i.e., 6 kHz) were quantified with a clinical audiometer (Madsen Midimate 622D; GN Otometrics, Denmark). Sennheiser HDA 2000 headphones (Sennheiser, Germany) were used for audiometric measurements, subsequent tinnitus matching and acoustic stimulation. Minimum masking level (MML) was assessed by increasing the loudness of a WN sound (Madsen Midimate 622D; GN Otometrics, Denmark) until their tinnitus was completely masked.

Table 1.

Sample characteristics.

	Total sample				Noise-like tinnitus				Tonal tinnitus					p
N (female)	29 (7)				14 (6)				15 (1)					**.03**
Tinnitus laterality (left/ right/ both)	4/ 4/ 21				4 / 3/ 7				0/ 1/ 14					.13
	Mean ± SD	**Md**	**Min**	**Max**	**Mean ± SD**	**Md**	**Min**	**Max**	**Mean ± SD**	**Md**	**Min**	**Max**	**t(df)/ U**	**p**
Age (years)	55.59 ± 9.51	57.00	22.00	71.00	58.50 ± 7.81	60.00	45.00	71.00	53.07 ± 10.44	54.00	22.00	66.00	1.59 (25.83)	.12
Tinnitus duration (months)	159.97 ± 92.72	161.00	20.00	420.00	119.86 ± 80.28	102.00	20.00	240.00	197.40 ± 90.00	190.00	60.00	420.00	**-2.45 (26.95)**	**.02**
Center frequency (Hz) – matching 1					5404.21 ± 1618.94	5399.00	1684.00	8301.00						
Center frequency (Hz) – matching 2					5483.07 ± 3748.85	4280.00	523.00	13298.00						
Tinnitus frequency (Hz) – matching 1									5395.27 ± 1893.54	5501.00	2796.00	9334.00		
Tinnitus frequency (Hz) – matching 2									5683.73 ± 1980.87	5617.00	2471.00	9766.00		
Tinnitus loudness (dBA) – matching 1	65.08 ± 13.41	69.56	40.75	84.61	55.98 ± 10.98	53.44	40.75	73.86	73.57 ± 10.29	75.15	52.36	84.61	**-4.66 (26.94)**	**< .01**
Tinnitus loudness (dBA) – matching 2	63.23 ± 14.14	63.54	36.88	84.61	53.87 ± 11.64	51.28	36.88	76.44	71.97 ± 10.93	71.71	45.91	84.61	**-4.31 (26.52)**	**< .01**
Matching 1 length (min)	11.07 ±4.46	11.00	4.00	19.00	13.50 ± 3.59	15.00	6.00	17.00	8.8 ± 4.06	8.00	4.00	19.00	**170.00**	**< .01**
Matching 2 length (min)	5.17 ± 2.45	5.00	2.00	14.00	6.29 ± 2.95	5.50	3.00	14.00	4.13 ± 1.25	4.00	2.00	6.00	**158.00**	**.02**
Hearing loss left (dB)	17.98 ± 9.99	17.27	2.73	38.64	19.16 ± 11.45	18.64	2.73	38.64	16.88 ± 8.67	17.27	4.09	33.18	.60 (24.19)	.55
Hearing loss right (dB)	17.27 ± 10.32	15.91	3.18	40.45	18.67 ± 11.79	15.91	3.64	40.45	15.97 ± 8.96	15.91	3.18	32.27	.69 (24.25)	.50
Minimum masking level (dB)	54.17 ± 16.84	55.00	20.00	80.00	47.43 ± 17.90	40.50	20.00	76.00	60.47 ± 13.47	57.00	41.00	80.00	**-2.20 (24.12)**	**.04**
Sensation level (dB) (1 missing value)	32.50 ± 19.08	35.00	5.00	70.00	31.54 ± 21.74	35.00	5.00	70.00	33.33 ± 17.18	35.00	5.00	55.00	-.24 (22.79)	.81
TQ total score (0-84)	33.28 ± 16.97	32.00	7.00	60.00	32.07 ± 16.03	31.00	7.00	60.00	34.40 ± 18.28	35.00	10.00	58.00	-.36 (26.90)	.72
THI total score (0-100)	39.03 ± 22.56	34.00	4.00	98.00	40.00 ± 24.09	36.00	6.00	98.00	38.13 ± 21.85	34.00	4.00	70.00	.22 (26.26)	.83
HQ9 (0-27)	11.31 ± 5.76	11.00	1.00	24.00	11.21 ± 4.81	11.50	5.00	20.00	11.40 ± 6.71	8.00	1.00	24.00	-.09 (25.28)	.93
VAS loudness (0-100)	45.00 ± 22.81	36.00	8.00	82.00	35.79 ± 21.90	30.00	8.00	82.00	53.60 ± 20.77	61.00	14.00	77.00	**57.00**	**.04**

Md = median; Min = minimum; Max = maximum; TQ = tinnitus questionnaire; THI = tinnitus handicap inventory; Mini-HQ9 = mini Hyperacusis questionnaire; VAS loudness = Visual Analog Scale tinnitus loudness.

Tinnitus Matching

In order to ascertain participants individual tinnitus pitch, the Method of Adjustment approach (Henry et al., 2013) was performed with a custom-made MAX application (MAX 7; Cycling'74, USA) together with a modular hardware controller (Palette Expert Kit; Palette, Canada). The matching procedure's steps were in accordance with the order within the Tinnitus Tester procedure (Roberts et al., 2008) with an additional test for octave confusion at the end. Prior to tinnitus matching, participants were asked to vocalize or describe their tinnitus to distinguish between noise-like and tonal tinnitus types as indicated in the recruiting process. Following on that, they were instructed and trained for the process of tinnitus matching. Parameters examined by the matching procedure were as follows: tinnitus frequency, respectively centre frequency for noise-like tinnitus (Hz), tinnitus loudness (dB) and tinnitus laterality (0 = left ear; 127 = right ear; thus a value of 63 describes a bilateral tinnitus). Control units of the matching controller were labelled accordingly. The step size of frequency dial was marginally below a semitone and ranged from 40 Hz to 16 kHz. For tonal tinnitus matching, a 3 kHz pure tone with comfortable loudness was set as a starting point, followed by an adjustment of the frequency by the participants to determine their individual tinnitus frequency. Finally, tinnitus loudness and laterality were adjusted with the matching controller to complete the matching procedure. In case of noise-like tinnitus, the starting sound was a filtered broadband noise (bandwidth: 1/3 octave of centre frequency). Participants were able to adjust the centre frequency of the noise and also the bandwidth of the filter settings according to their individual tinnitus noise. Subsequently, loudness and laterality were identified just as with the pure tone matching. Finally, participants rated the agreement of their tinnitus with the matched sound on a 1–10 scale. To assess individuals' sensation level (SL), the hearing threshold of the frequency next to the individual tinnitus frequency or centre frequency was used (i.e., stepping down to the next lower frequency. For example, if the individual tinnitus frequency was 7.4 kHz, the hearing threshold at 7 kHz was investigated). The matching procedure was repeated after the acoustic stimulation block of the experiment.

Acoustic Stimulation

Seven different modified noise stimuli were created in MATLAB (Matlab R2015a; Mathworks, Natick, MA, USA) and utilized for a 3 min acoustic stimulation with an intensity of 60 dB SL. Stimuli set consisted of unmodified WN, WN with AM rates at 10 Hz (WN10) and 40 Hz (WN40), as well as a IBP with the same modulation rates (IBP, IBP10, IBP40). BP width was set according to the matching results in noise-like tinnitus participants. In participants with tonal

tinnitus, the previously matched individual tinnitus pitch was used to deploy an IBP to WN with a range of one octave (Pantev et al., 2012). Furthermore, an IBP WN with 10 Hz AM rates at MML intensity (IBP10_MML) was used for acoustic stimulation in order to contrast SL and MML. Acoustic stimulation was conducted in a randomized order for each session with a maximum loudness of 80 dBSPL diotically over the headphones. If participants experienced discomfort, they were able to stop the stimulation and experimental procedures at any time. Following a 3-minute stimulation for each stimulus, participants evaluated their tinnitus loudness (%) in comparison to prior the particular stimulation on a numeric rating scale (0% up to 140% in 10% steps) at 7 different points in time (0, 30, 60, 90, 120, 150 and 180 s after stimulation offset). Moreover, participants rated the induced valence and arousal of each single stimulus with pictorial manikin scales (Bradley and Lang, 1994).

Statistical Analysis

All statistical analyses were performed using the statistic software R (R version 3.4.3; R Foundation for Statistical Computing, Austria) and the packages "psych," "emmeans," "sjstats," and "lme4." Tinnitus loudness and stimulus evaluation data were analysed by means of linear mixed effect models for each dependent variable denoted as response (tinnitus loudness, valence, arousal). Potential Models were compared with Likelihood Ratio Tests in a step-wise selection approach (Harrison et al., 2018). Following predictors as well as their interactions were tested in the model fitting procedure: condition (stimuli used; see acoustic stimulation section), group (noise-like tinnitus, tonal tinnitus), time (0, 30, 60, 90, 120, 150, 180 s after stimulation end), gender (male, female), age, tinnitus duration, tinnitus loudness (according to first tinnitus matching), MML and tinnitus distress (TQ sum score). The proportion of explained variance was identified by marginal (variance of the fixed effects) and conditional (variance of fixed and random effects) R^2 (Nakagawa et al., 2017). In any of the fitted models, the participant (id) was treated as a random effect. Fixed effects of the final model were tested via expected mean square approach. Post-hoc Tukey tests were calculated to contrast responses for condition and group. In order to test for a potential bias due to the sequence of the stimuli used for acoustic stimulation (position effect), a median split was conducted on the positions variable and differences in means were then tested with Student t-tests.

Analysis of descriptive group differences (noise-like vs. tonal tinnitus) for parametric variables was done by the means of two-sample t-tests. In case of violation of normal distribution and homoscedasticity, non-parametric testing via independent sample Mann-Whitney U-tests was

used. Categorical data was analyzed by Fisher's exact tests, due to cell frequencies below 5 in all variables.

Reliability for the matching procedure (between first and second matching round) was assessed via Pearson correlations, or rather Spearman correlations in case of a violation of normal distribution, for tinnitus loudness and tinnitus or centre frequency. Statistical significance was defined as $p \leq .05$ for all analysis.

Results

Participant Characteristics

Demographic and clinical characteristics for the whole study sample and for tinnitus sub-groups (noise-like and tonal tinnitus) can be found in **Table 1**. A Fisher's exact test was able to identify a significant association between gender and the type of tinnitus. In the group with tonal tinnitus the proportion of female participants was significantly lower ($p = .03$). Statistical testing revealed significant differences in terms of tinnitus duration and subjective rating of tinnitus loudness (VAS loudness), with the noise-like tinnitus group showing a shorter duration of tinnitus ($t_{(26.95)} = -2.45$, $p = .02$) and evaluating their tinnitus loudness lower ($U = 57.00$, $p = .04$). Further, no differences were found in TQ ($t_{(26.90)} = -.36$, $p = .72$), Tinnitus Handicap Inventory ($t_{(26.26)} = .22$, $p = .83$) or HQ9 ($t_{(25.28)} = -.09$, $p = .93$) scores among the 2 subgroups.

Audiometry and Tinnitometry

Table 1 shows audiometric and tinnitus matching results with a significant lower tinnitus loudness (corresponding with subjective loudness rating; see the descriptives section above) for both matching procedures (matching 1: $t_{(26.94)} = -4.66$, $p < .01$; matching 2: $t_{(26.52)} = -4.31$, $p < .01$) and MML ($t_{(24.12)} = -2.20$, $p = .04$) in the group of noise-like tinnitus. On the basis of a consolidation of these audiometric and tinnitometric findings, **Figure 1** indicates an overlap of tinnitus frequency with the frequency of HL. As might be expected, the length of the first and second matching process was significantly shorter in the tonal tinnitus group (cf. **Table 1**). Mean HL difference for both ears were not significantly different between groups (left: $t_{(24.19)} = .60$, $p = .55$; right: $t_{(24.25)} = .69$, $p = .50$). In both groups, the HL was more pronounced on the left side. There were positive significant correlations between the first and the second matching for tinnitus loudness (noise-like: $r = .77$, $p < .01$; tonal: $r = 0.73$, $p = < .01$) in both groups. With respect to tinnitus/ centre frequency a positive significant correlation was only observed in the tonal tinnitus group (noise-like: $r = .14$, $p = .64$; tonal: $r = .65$, $p = < .01$).

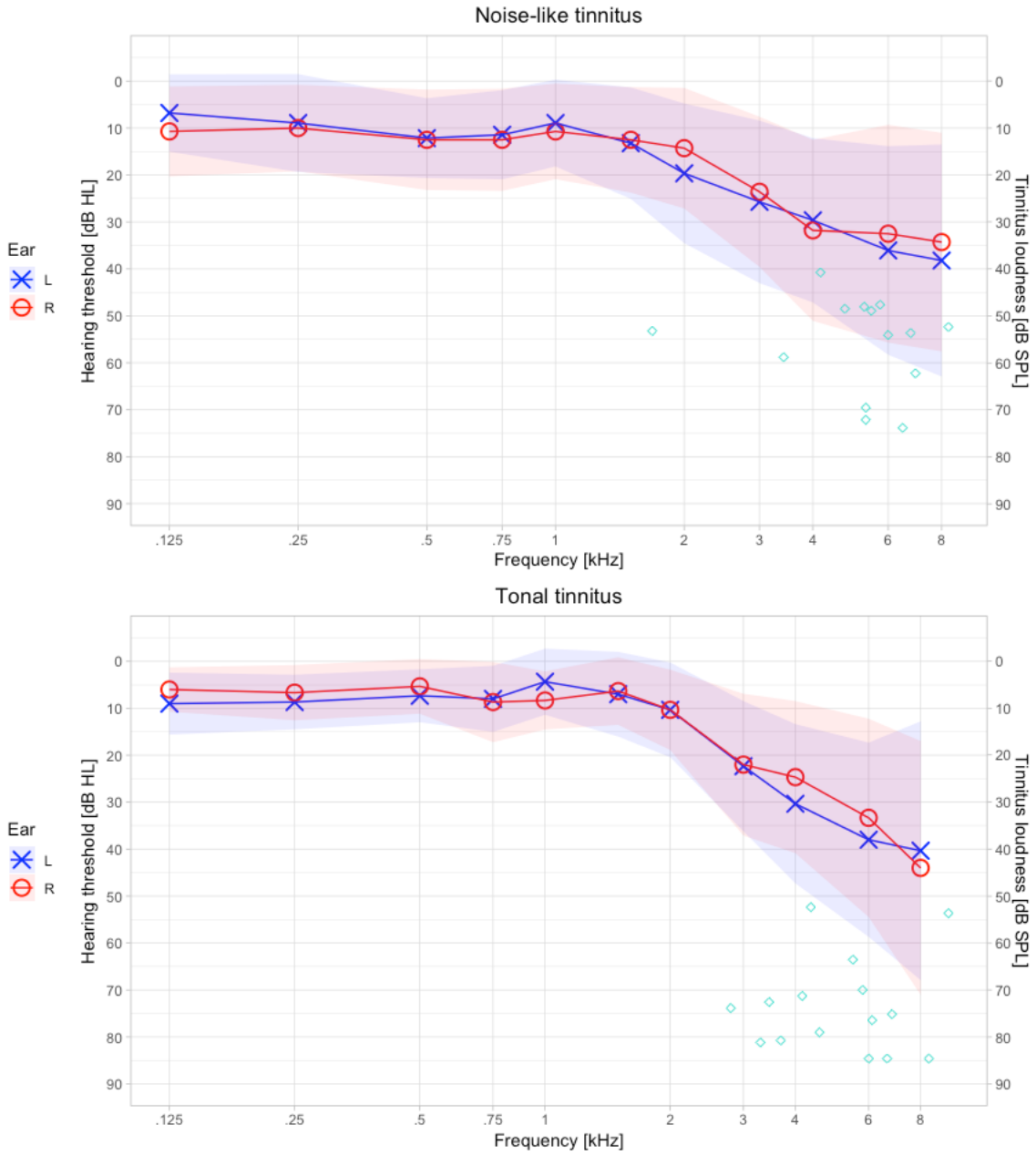

Figure 1. **Audiometry and Tinnitometry.**
Audiometric measurement results for both ears together with individual tinnitus frequency (i.e., centre frequency of the IBP) and loudness as identified by tinnitus matching split for noise-like and tonal tinnitus. It should be noted, that tinnitus/ centre frequency overlaps with the frequencies of HL. HL = hearing loss.

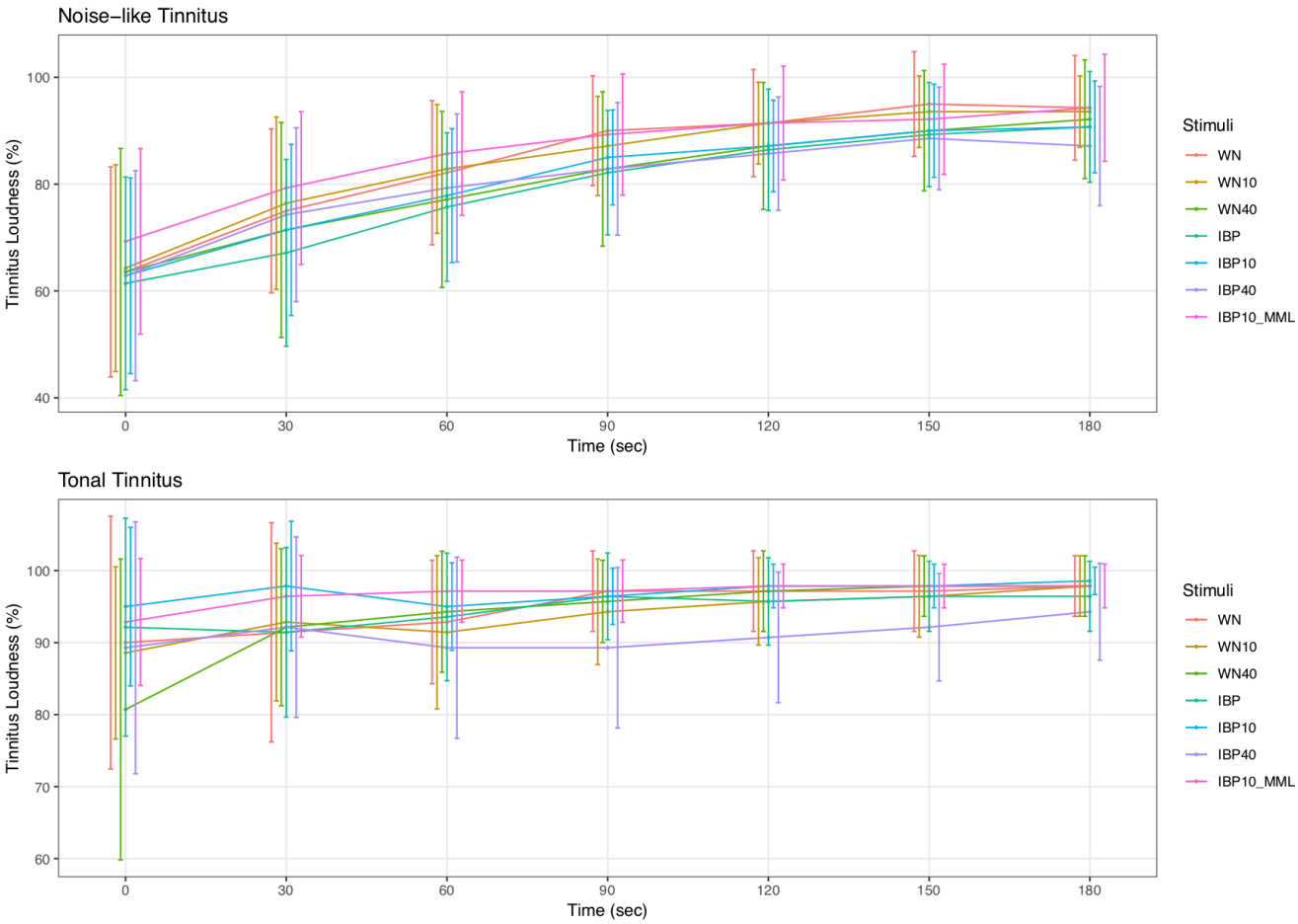

Figure 2. **Tinnitus loudness time curve split by group**.
For each stimulus the tinnitus loudness rating over all time points is plotted separated for noise-like and tonal tinnitus (CIs at 95% shown as brackets). Overall, each stimulus was able to suppress tinnitus loudness (cf. supplemental material Table S1). In terms of suppression averaged over time but also at T0, stimulus IBP appeared to produce the strongest.

Acoustic Stimulation

Prima facie, the stimulus IBP40 appeared to produce the strongest tinnitus suppression regardless of group and time (M = 86.16, SD = 25.60), whereas at time point T0 (immediately after stimulation offset), WN40 induced the lowest tinnitus loudness (M = 73.10, SD = 41.76). Descriptive statistics for the 7 utilized stimuli averaged over time and for time point T0 are listed in supplementary **Table S1** for the whole sample and divided for subgroups. **Figure 2** shows the time curve for all stimuli with respect to tinnitus loudness ratings, in the same manner supplementary **Figure S1** provides information about single subject responses for each stimulus. No confounding effect caused by the order of the stimuli in the stimulation sequence was detected by our analysis ($t_{(1215.60)} = .09$, $p = .93$) and therefore stimuli order was not entered in the final model fitting procedure. In accordance with the previous described model fitting approach (cf. section statistical analysis in methods part), we were able to identify the following model with the best fit to our data: *response ∼condition + time*group + (1|id)*. Detailed results of the model fitting are outlined in supplementary **Table S2**. By testing the fixed effects of the

model via expected mean square approach, significant effects for condition, time, group and for the interaction time*group on tinnitus loudness were observed (cf. **Table 2**). Subsequent post-hoc contrasts for condition failed to find statistically significant differences in tinnitus loudness ratings with respect to the applied stimuli (**Table 3**).

Table 2.
Fixed effect testing

	numDF	denDF	F	p
Condition	6.00	1392.00	3.35	< .01
Time	6.00	1392.00	39.84	< .01
Group	1.00	29.00	5.04	.03
Time*Group	6.00	1392.00	15.17	< .01

numDF = degrees of freedom numerator; denDF = degrees of freedom denominator.

Table 3.
Post-hoc Tukey contrasts for condition

Contrast	Estimate	t	p
IBP – IBP10	-1.53	-1.06	.94
IBP – IBP10_MML	-4.38	-3.05	.04
IBP – IBP40	1.08	.75	.99
IBP – WN	-2.76	-1.92	.47
IBP – WN10	-2.17	-1.51	.74
IBP – WN40	-.34	-.24	> .99
IBP10 – IBP10_MML	-2.86	-1.98	.42
IBP10 – IBP40	2.61	1.81	.54
IBP10 – WN	-1.23	-.86	.98
IBP10 – WN10	-.64	-.44	> .99
IBP10 – WN40	1.18	.82	.98
IBP10_MML – IBP40	5.47	3.80	< .01
IBP10_MML – WN	1.63	1.13	.92
IBP10_MML – WN10	2.22	1.54	.72
IBP10_MML – WN40	4.04	2.81	.08
IBP40 – WN	-3.84	-2.67	.11
IBP40 – WN10	-3.25	-2.26	.27
IBP40 – WN40	-1.43	-.99	.96
WN – WN10	.59	.41	> .99
WN – WN40	2.41	1.68	.63
WN10 – WN40	1.82	1.27	.87

Degrees of freedom = 1410.23; SE = 1.44; IBP = individualized bandpass filtered; MML = minimum masking level; WN = white noise.

Interestingly, a significant difference in tinnitus loudness ratings between the 2 subgroups was revealed independently of condition and time as exemplified in **Table 4** and **Figure 3** (noise-like: M = 82.14, SD = 26.68; tonal: M = 94.79, SD = 16.44; $t_{(31.15)} = 2.17$, $p = .04$). On the basis of a significant interaction among group and time, we contrasted the mean tinnitus loudness for each group for all 7 time points after stimulation. Our results point out a significant difference between the groups only at T0 (noise- like: M = 63.98, SD = 36.49; tonal: M = 90.19, SD = 28.01; $t_{(38.40)} = 4.27$, $p < .01$; cf. **Table 5**).

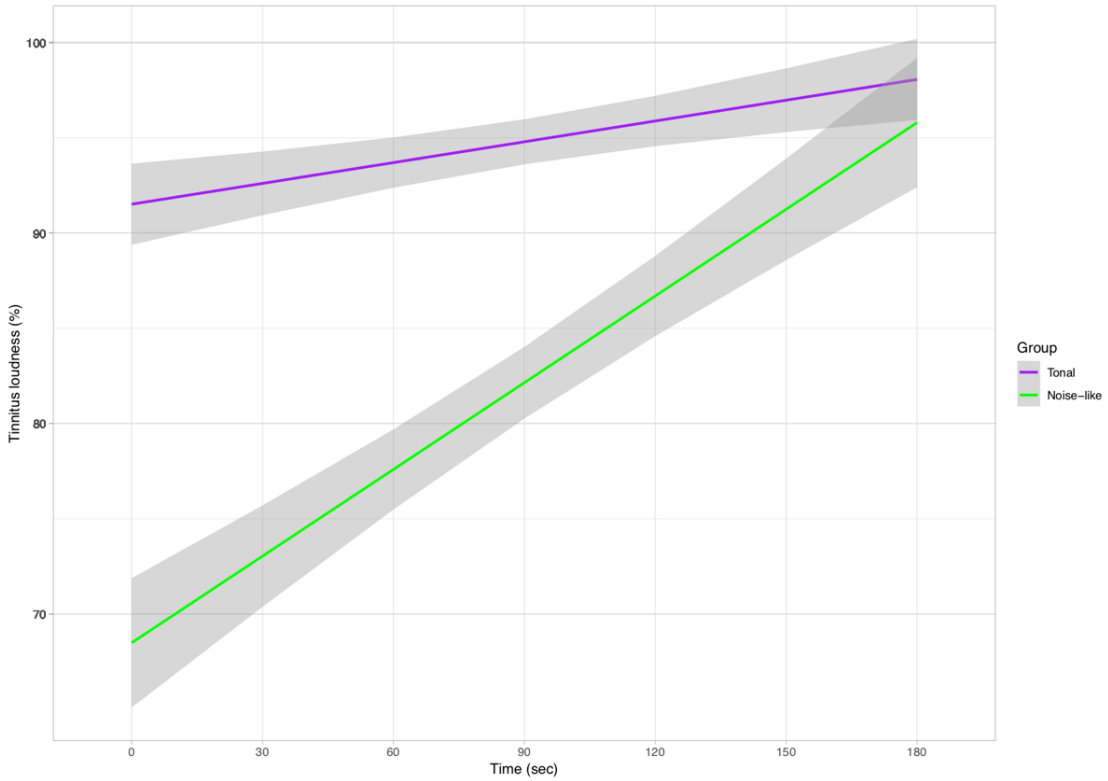

***Figure 3*. Mean suppression differences between groups.**
Time curve of the averaged tinnitus suppression values split for tonal and noise-like tinnitus. SD for the mean suppression data of each group is plotted as a grey ribbon. Differences between the 2 subgroups were found to be significant.

Table 4.
Post-hoc Tukey contrasts for group.

Contrast	Estimate	t	p
Tonal vs. noise-like	**12.65**	**2.17**	**.04**

Degrees of freedom = 31.15; SE = 5.84.

Table 5.
*Post-hoc Tukey contrasts for group*time.*

Contrast		Estimate	t	p
Tonal vs. noise-like	**Time**			
	0	**26.21**	**4.27**	**< .01**
	30	20.05	3.27	.10
	60	13.61	2.22	.62
	90	9.91	1.62	.93
	120	7.61	1.24	> .99
	150	5.54	.90	> .99
	180	5.59	.91	> .99

Degrees of freedom = 38.40; SE = 6.13.

Stimulus Evaluation

Arousal

As pointed out in supplementary **Table S3** and **Figure 4**, emotional stimuli evaluation for the whole group identified the highest arousal ratings for stimulus IBP40, while IBP10_MML expectably manifested in the lowest arousal values. Model fitting proceedings identified the subsequent model with the best fit for our arousal data: *response ~ condition + (1|id)* (cf. supplemental **Table S4**). Fixed effect testing detected a significant effect for condition (cf. **Table 6**). Ensuing post-hoc contrasts revealed significant differences in arousal ratings for IBP versus IBP40 ($t_{(180.21)}$ = -3.08, p = .04), IBP10 vs. IBP10_MML ($t_{(180.21)}$ = 2.98, p = .05), IBP10_MML versus IBP40 ($t_{(180.21)}$ = -4.33, p < .01), IBP10_MML versus WN10 ($t_{(180.21)}$ = -3.66, p < .01), and IBP10_MML vs. WN40 ($t_{(180.21)}$ = -4.04, p < .01). Post-hoc analysis results are reported in **Table 7**; relevant significant results are highlighted in bold.

Valence

In line with the descriptive arousal results, IBP10_MML had the highest ratings for valence, whereas stimulus WN40 was evaluated with the least valence (cf. supplemental material **Table S3**; **Figure 4**). Same model structure was fitted as for the arousal data (cf. supplemental material **Table S4**) and likewise a significant effect of condition was found (cf. **Table 6**). Post-hoc results are listed in **Table 7** and demonstrate a significant difference for IBP10_MML versus WN40 ($t_{(180.21)}$ = 3.78, p < .01).

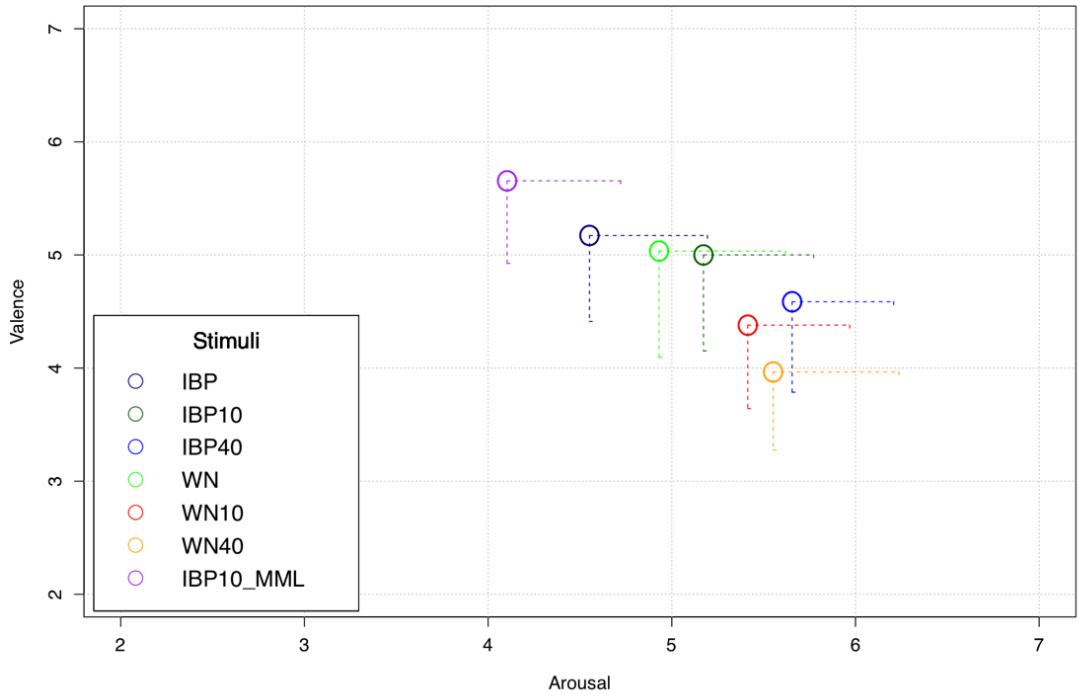

***Figure 4*. Valence and arousal rating per stimuli.**
Parentheses show 95% CI for arousal and valence ratings for all stimuli. Lowest tolerability was found in WN40 as indicated by high arousal and low valence stimulus evaluation, whereas stimulus IBP10_MML shows the highest tolerability. WN = white noise; MML = minimum masking level; IBP = individualized bandpass filtered.

Table 6.
Fixed effect testing – arousal and valence.

	numDF	denDF	F	p
Arousal				
Condition	6.00	174.00	5.17	< .01
Valence				
Condition	6.00	174.00	3.25	< .01

numDF = degrees of freedom numerator; denDF = degrees of freedom denominator.

Table 7.
Post-hoc Tukey contrasts for condition.

	Arousal			Valence		
Contrast	**Estimate**	**t**	**p**	**Estimate**	**t**	**p**
IBP – IBP10	-.62	-1.73	.60	-.17	.39	>.99
IBP – IBP10_MML	.45	1.25	.87	-.48	-1.08	-93
IBP – IBP40	-1.10	**-3.08**	**.04**	.59	1.31	.85
IBP – WN	-.38	-1.06	.94	.14	.31	>.99
IBP – WN10	-.86	-2.41	.20	.79	1.77	.57
IBP – WN40	-1.00	-2.79	.08	1.21	2.70	.10
IBP10 – IBP10_MML	1.07	**2.98**	**.05**	-.66	-1.47	.76
IBP10 – IBP40	-.48	-1.35	.83	.41	.93	.97
IBP10 – WN	.24	.67	.99	-.03	-.08	>.99
IBP10 – WN10	-.24	-.67	.99	.62	1.39	.81
IBP10 – WN40	-.38	-1.06	.94	1.03	2.32	.24
IBP10_MML – IBP40	-1.55	**-4.33**	**<.01**	1.07	2.39	.21
IBP10_MML – WN	-.83	-2.31	.25	.62	1.39	.81
IBP10_MML – WN10	-1.31	**-3.66**	**.01**	1.28	2.86	.07
IBP10_MML – WN40	-1.45	**-4.04**	**<.01**	1.69	**3.78**	**<.01**
IBP40 – WN	.72	2.02	.41	-.45	-1.00	.95
IBP40 – WN10	.24	.67	.99	.21	.46	>.99
IBP40 – WN40	.10	.29	>.99	.62	1.39	.81
WN – WN10	-.48	-1.35	.83	.66	1.47	.76
WN – WN40	-.62	-1.73	.60	1.07	2.39	.21
WN10 – WN40	-.14	-.38	>.99	.41	.93	.97

Arousal: degrees of freedom = 180.21; SE = .36; Valence: degrees of freedom = 180.21; SE = .45
IBP = individualized bandpass filtered; WN = white noise; MML = minimum masking level.

Discussion

The aim of the present study was to investigate the effects of different IBP and AM noise stimuli on RI in people with tonal and noise-like tinnitus. To the best of our knowledge, no former study has systematically investigated the deployed acoustic stimulation procedures, especially neither AM nor IBP sounds, in noise-like tinnitus cases. A parametric noise-band matching approach was applied in order to personalize BP settings in accordance with the tinnitus characteristics in the group with noise-like tinnitus, whereas the group with tonal tinnitus matched their tinnitus via the centre frequency of a fixed filter band-width. Taken together, all these aspects constitute novel lines of investigation within tinnitus research. Omnibus results of our experiment emphasize the ability of all used noise stimuli in inducing RI (cf. **Table 2**). The time courses and different suppression patterns for each stimuli appear in a similar manner as in previous studies, in that they generally converge over time after an initial maximum of

suppression (Feldmann, 1983; Neff et al., 2017, 2019b; Roberts, 2007; Roberts et al., 2008; Vernon and Meikle, 2003).

Contrary to our hypotheses, no statistically significant differences between the various stimuli and their impact on tinnitus perception respectively RI was observed. In more detail, neither the customization of the noise bands nor the AM resulted in significant differences between the conditions (i.e., stimuli). This outcome is in conflict with findings of earlier studies, which have suggested advantages of AM pure tones for RI (Neff et al., 2017, 2019b; Reavis et al., 2012; Tyler et al., 2014). Yet, looking at these studies, pure tones were only compared to AM pendants with the exception of Tyler et al. (2014), who contrasted AM pure tones with unmodulated broadband noise.

A potential explanation for the lack of advantage of AM stimuli could be attributed to the circumstances, that noise is inherently composed of a wide spectrum of frequencies and signal-inherent amplitude modulation rates. These may cover up or neutralize the potential effects of certain AM rates for RI.

To the best of our knowledge, no former study specifically tested RI or sound therapies in entities with noise-like tinnitus. Of special interest, our analysis revealed statistical differences in RI for the subgroups noise-like and tonal tinnitus, with the noise-like group demonstrating larger RI than the tonal group. These significant differences were only observed immediately after the stimulation, suggesting a time-limited advantage of noise stimuli for RI in noise-like tinnitus. The reason for this group-difference is not clear, and a possible rationale may be due to physiological differences between these two groups with a supposed additional contribution of the extralemniscal system in noise-like tinnitus (Møller, 2006). A further potential confounding factor for this group effect might be the fact that tinnitus loudness as elicited by MML, tinnitus matching and also in subjective ratings via VAS scales was found to be significant higher in the tonal subgroup. On the other hand, with no meaningful difference in HL between the groups and in consequence similar SLs, the putative confounding influence of these measures may play a negligible role. An in-depth analysis of the noise-like tinnitus group exclusively, demonstrated no statistical differences in tinnitus loudness ratings with respect to the used stimuli in a similar fashion as the analysis of the whole study sample.

However, since the bandwidth of BP filter settings in participants with tonal tinnitus was set to a range of one octave around the individual tinnitus frequency, whereas participants with noise-like tinnitus were able to individually adjust the BP filter settings, the differences in the subgroups may also derive from discrepancies in stimuli creation. It was expected that a stimulation with noise is more pleasant or tolerable than a stimulation with pure tones. Unlike

this assumption, our findings reveal a similar tolerability pattern for AM noise stimuli as Neff et al. (Neff et al., 2019b) on the basis of AM pure tones (cf. **Figure 4**). The analysis conducted also show, that AM might lead to more arousal as indicated on a descriptive level as well as the significant difference between IBP and IBP40 (cf. **Table 7**). As must be expected, the lower intensity stimulus (IBP10_MML) had the lowest arousal and highest valence ratings.

Our results indicate that the used matching method is feasible for determining tinnitus characteristics. In detail there was good consistency for both tinnitus loudness and frequency for both matching trials in noise-like and tonal tinnitus groups. These findings are in line with Henry et al. (Henry et al., 2013), who already reported test-retest reliability for noise-band tinnitus matching.

Limitations

The generalizability of these results is subject to certain limitations. As already discussed above, the significantly lower tinnitus loudness in the group of noise-like tinnitus could weaken our findings of subgroup differences in short-term tinnitus suppression.

However, as no difference in HL and equality in SL were observed, this may not play a significant role. Likewise, the sample size of this experiment is rather small and gender ratio in the subgroups is unbalanced. One main issue is the impossibility to control for potential participant-related failures in noise-band matching. But for all of that, unavailable validation of the quantification of peoples' tinnitus characteristics represents a common problem in tinnitus matching approaches, as it is a subjective phenomenon. Future studies should strive for new possibilities in verifying tinnitus matching results, as well as optimization of given methodological approaches.

Since we did not compare tonal and noise stimuli, it is not possible to make a statement about a general superiority of noise stimuli in short-term tinnitus suppression in noise-like tinnitus.

Conclusion

The current study demonstrates a general efficacy of noise stimuli with different AM rates and filtering strategies for RI. Contrary to our expectations, no differences between the types of stimuli were observed. There were differences in RI among the subgroups of noise-like and tonal tinnitus, with better performance directly after the stimulation in the noise-like tinnitus group, were observed. Although, no stable rationale for the group differences can be provided, the findings may provide insights in the mechanism of RI for different tinnitus types. Future studies with larger sample sizes, improved matching/ audiometry procedures and more acoustic

stimulation repetitions per stimuli are needed to investigate these potential differences in more detail in order to enhance our understanding of the effects of acoustic stimulation on tinnitus perception. Taken together these results illustrate the potential of noise-stimuli in short-term tinnitus suppression, especially in entities with noise-like tinnitus.

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Disclosure statement

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Author contributions

The authors P.N., W.S., and S.S. designed the study. J.A. collected the data. S.S. and P.N. analysed the data and wrote the main manuscript. All authors contributed to and reviewed the manuscript.

4. Study 2 – Neurophysiological correlates of residual inhibition in tinnitus: Hints for trait-like EEG power spectra

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Abstract

Background: Magneto- and electroencephalography (M/EEG) investigations in tinnitus patients demonstrated anomalous oscillatory brain activity patterns compared to healthy controls. A well-established phenomenon in tinnitus is the possibility to temporary suppress tinnitus following acoustic stimulation, which is termed residual inhibition (RI). The few former neurophysiological investigations of RI reported partly conflicting results hampering consensus on tinnitus-specific brain activity and basic neural models. **Objectives:** Hence, our objective was to investigate RI-specific oscillatory brain activity changes and whether these changes can be associated with behavioral measures of tinnitus loudness. Further, contrasts between acoustic stimulation responders and non-responders provide further insights in RI-related spontaneous brain activity. **Methods:** Three different types of noise stimuli were administered for acoustic stimulation in 45 tinnitus patients. Subjects resting state brain activity was recorded before and during RI via EEG alongside with subjective measurements of tinnitus loudness. **Results:** On the whole-group level, tinnitus-unspecific changes were observed which fit established knowledge about basic neural responses after acoustic stimulation. Responder non-responder contrasts revealed differences in alpha and gamma band activity in line with the proposed neural models for oscillatory brain activity in tinnitus. Further analysis of sample characteristics demonstrated divergences between responders and non-responders notably for tinnitus duration. During RI, distinct differences between responders and non-responders were exclusively observed for alpha band activity in auditory cortical areas. Neither correlations of behavioral tinnitus measures nor differences between stimulus-induced changes in ongoing brain activity could be detected. **Conclusion:** Taken together, our observations might be indicative of trait-specific forms of oscillatory signatures in different subsets and chronification grades of the tinnitus population possibly related to acoustic tinnitus suppression. Results and insights are not only useful to understand basic neural mechanisms behind RI but are also valuable for general neural models of tinnitus.

Introduction

Subjective tinnitus is defined as the perception of a ringing or hissing without the presence of a corresponding internal or external source of sound. If this phantom sound perception is present over a period of at least six months, it is considered as chronic (Mazurek et al., 2010). About 10 – 15% of the global population suffers from tinnitus, whereas in 1 – 2% it represents a severe burden (Erlandsson and Dauman, 2013; Heller, 2003; Langguth et al., 2013) with comorbidities such as depression, anxiety disorder, sleep disorder or reduced quality of life (Croenlein et al., 2016; Nondahl et al., 2007; Trevis et al., 2016; Weidt et al., 2016). Currently there is no treatment option for tinnitus available. A major challenge towards an identification of a treatment is related to heterogeneity in tinnitus phenotypes (Cederroth et al., 2019; Hesse, 2016; Kleinjung and Langguth, 2020; Zenner et al., 2017). Up to now, cognitive behavioral therapy represents the treatment option with the best available evidence for tinnitus (Cima et al., 2012; Fuller et al., 2020; Landry et al., 2020; J. Li et al., 2019).

In the majority of cases, tinnitus develops as a consequence of cochlear damages subsequent to noise trauma or hearing loss (HL) (Langguth et al., 2013). Typically, the perceived tinnitus pitch corresponds to the frequency range of maximum HL (Basile et al., 2013; Norena et al., 2002; Roberts et al., 2008; Schecklmann et al., 2012). Theories about the generation of tinnitus commonly suggest that the reduced or missing auditory input triggers maladaptive alterations along the auditory pathway and the central auditory system, which may lead to the sensation of a phantom sound in the frequencies of the peripheral HL (Adjamian et al., 2009; Eggermont, 2007; Eggermont and Roberts, 2012; Eggermont and Tass, 2015).

On a macroscopic level tinnitus was associated with anomalous oscillatory brain activity patterns such as enhanced activity in the delta and gamma frequency range alongside with reduced alpha activity over temporal regions (Weisz et al., 2007b, 2005). As observed in several neurophysiological investigations, this delta increase and alpha decrease appears to be closely linked to tinnitus perception as well as tinnitus distress (Adjamian et al., 2012; Balkenhol et al., 2013; Moazami-Goudarzi et al., 2010; Schlee et al., 2014; Weisz et al., 2005). Due to relations with tinnitus loudness as defined via tinnitus pitch matching (Balkenhol et al., 2013), subjective tinnitus loudness (De Ridder et al., 2015a; van der Loo et al., 2009) or tinnitus-specific increased activity in the auditory cortex (Ashton et al., 2007; S. Vanneste et al., 2011), high gamma activity was proposed to represent the oscillatory signature of tinnitus perception per se (Weisz et al., 2007b).

These tinnitus-specific spontaneous brain activity patterns were subsumed under the framework of the thalamo-cortical dysrhythmia model (TCD) (De Ridder et al., 2015b; Llinás et al., 2005,

1999), which was further expanded to the "Synchronization-by-Loss-of-Inhibition-Model" (SLIM) (Weisz et al., 2007a).

Conversely, some studies neither observed altered delta and alpha activity in tinnitus (Ashton et al., 2007) any power spectra differences compared to healthy controls (Zobay et al., 2015) nor correlations between electrophysiology and psychoacoustic or psychosocial tinnitus measures (Pierzycki et al., 2016). In the same vein, further studies report higher alpha activity in tinnitus (Moazami-Goudarzi et al., 2010), a relationship of enhanced alpha and tinnitus intensity (Meyer et al., 2014) or emphasize the relevance of other frequency bands like beta and theta in neural activity related to tinnitus (Balkenhol et al., 2013; Meyer et al., 2014; Moazami-Goudarzi et al., 2010). Considering these observations, assumptions about abnormal tinnitus-specific respectively tinnitus-related spontaneous brain activity are not so conclusive as presumed initially.

The phenomenon of short-term tinnitus suppression following acoustic stimulation was first studied almost 50 years ago (Feldmann, 1983, 1971). This phenomenon was defined as "residual inhibition" (RI) and can be observed in 60 – 80% of tinnitus sufferers, whereby depth and duration of suppression patterns vary among individuals (Roberts, 2007; Roberts et al., 2006; Vernon and Meikle, 2003). Since that time several experiments already examined the impact of various auditory stimulation techniques on RI. These vary from simple white noise (WN) or pure tones, to the application of specific filters or modulation rates, up to the combination of both modulation techniques applied to WN (Fournier et al., 2018; Henry et al., 2013; Neff et al., 2017, 2019b; Reavis et al., 2012; Roberts et al., 2006, 2008; Schoisswohl et al., 2019b; Tyler et al., 2014). It has been suggested that stimulation intensity, duration, specific modulations as well as stimuli including the individual tinnitus frequency (ITF) facilitate short-term acoustic tinnitus suppression.

Another approach to reduce subjective tinnitus loudness for a longer period of time is provided via long-term stimulation with notch filtered music (individual tinnitus pitch is removed from the signal), referred to as "tailor-made notched music training" (TMNMT). The supposed underlying physiological effect behind TMNMT takes place through an inhibition of frequencies within the notch filter called lateral inhibition. By means of long term applications, maladaptive pathological reorganization of the auditory cortex in tinnitus may be reversed (Okamoto et al., 2010; Pantev et al., 2012).

Nevertheless, little is known about the basic neurophysiological processes behind RI (Roberts, 2007). Reduced firing rates of neurons in the central auditory pathway are theorized to play a

key role in RI (Galazyuk et al., 2019, 2017) which covers subcortical structures of the auditory system.

There is a paucity in experimental studies examining oscillatory brain activity after acoustic stimulation or rather during RI. With the help of neuromagnetic measures in one tinnitus subject (Kristeva-Feige et al., 1995) observed an increase in low frequency (2 – 8 Hz) spectral power during RI. Contrary to this observation, single-subject intracranial recordings showed a reduction of low frequency (delta: 1 – 4 Hz; theta: 4 – 8 Hz) activity in the auditory cortex during RI. These tinnitus-related low frequency oscillations also interacted with alpha (8 – 12 Hz), beta (20 – 28 Hz) and gamma (> 30 Hz) activity (Sedley et al., 2015). Beyond that, tinnitus intensity during RI was identified to be connected to delta (1.5 – 4 Hz), theta (4 – 8 Hz) and gamma (30 – 150 Hz) oscillatory activity in the auditory cortex by the use of single patient measurements of neuromagnetic brain activity.

The relevance of auditory gamma band activity for RI respectively tinnitus perception could be further corroborated by means of an inverse correlation with tinnitus intensity exclusively in tinnitus subjects experiencing residual excitation (Sedley et al., 2012).

Kahlbrock and Weisz (2008) evaluated neuromagnetic activity in 10 tinnitus patients experiencing RI, defined as 50% of tinnitus loudness reduction for 30 seconds after stimulation offset. A reduction of delta (1.3 – 4 Hz) activity in temporal areas was observed during RI, whereas the gamma band (low: 30.5 – 49 Hz; high: 50.3 – 70.2 Hz) was not affected (Kahlbrock and Weisz, 2008).

The authors conclude that during a short-term reduction of tinnitus intensity, tinnitus-related abnormal oscillatory activities are temporary reversed resulting in a restored balance of neural inhibitory and excitatory processes. A recent study from King et al. (2020) investigated ongoing electrophysiological brain activity of 30 tinnitus subjects following broad band noise stimulation. 17 participants were able to experience RI, whereby a comparison of RI with a control auditory stimulation condition without the ability to induce RI revealed differences with respect to ongoing brain activity. In detail, the authors report higher power in the alpha and gamma frequency bands over the course of RI compared to the control condition.

To the best of our knowledge, the above mentioned five studies represent the only attempts to investigate resting state oscillatory brain activity in the context of RI. The fact that available findings are inconsistent and that merely two experiments - one utilizing magnetoencephalography (MEG) and one Electroencephalography (EEG) - analyzed spontaneous brain activity during RI on a group level indicates an urgent need for respective research whether it is by means of MEG or EEG. Besides single subject analysis, group level

analyses represent a basic pillar in science in order to make more general statements about the investigated population e.g., ongoing brain activity associated with RI. Previous research utilizing neurophysiological measurements, used only one type of non-personalized sound and did not compare participants with and without RI.

In the course of this study we are employing an extended set of modified and personalized noise stimuli targeting putatively differential neural mechanisms (i.e., RI and lateral inhibition). Thus the main purpose of this EEG experiment was to examine oscillatory brain activity changes during RI (pre vs. post) following a stimulation with different types of noise. Moreover, we aimed to investigate, whether these changes are related to subjective tinnitus loudness ratings. Since RI is a phenomenon which cannot be induced in all people with tinnitus, differences in spontaneous brain activity between people who reported RI and those who didn't were analyzed (responders vs. non-responders). Apart from the efficacy of each used stimulus type in short-term tinnitus suppression on a group level, we hypothesize that filtered noise would result in stronger suppression patterns compared to unfiltered noise.

In detail, bandstop-filtered noise is assumed to produce the strongest effect via a potentially suppression of neurons reacting to frequencies within the filter range as already shown in long-term applications via TMNMT (Okamoto et al., 2010; Pantev et al., 2012). Due to the lack of past research in this field, we have no direct stimulus-specific a priori hypothesis about the types of changes from pre to post auditory stimulation in ongoing brain activity. However, we assume that potential changes in spontaneous brain activity can be associated with subjective tinnitus loudness ratings after stimulation. In accordance to Kahlbrock and Weisz (2008) we expect a decrease in delta and gamma activity as well as an increase in alpha activity from pre to post auditory stimulation in tinnitus cases experiencing RI (responders).

Further we anticipate spectral power differences in the respective frequency bands between acoustic stimulation responders and non-responders. In order to link these differences to auditory cortical activation, source localization of the EEG data was performed.

Methods

Participants

In the course of this study, N = 45 (14 female) patients with chronic subjective tinnitus (> 6 months tinnitus duration) were recruited from the Interdisciplinary Tinnitus Centre Regensburg, Germany. For participation, patients had to fulfill the following primary inclusion criteria: age between 18 and 75 years; absence of other causes for tinnitus e.g., Meniere's disease, otosclerosis or acoustic neurinoma; no infection of the oropharynx; no present somatic,

neurological or psychiatric disorder; no intake of psychoactive medication (e.g., antidepressants or anticonvulsant drugs), respectively substance or alcohol abuse at least 12 weeks before the start of the experiment; no hypersensitivity to sound; no tinnitus frequency < 1 kHz; no concurrent participation in other tinnitus-related studies or start of any other tinnitus-related treatment in the last three months prior study start. Ethical clearance with respect to methodological approach and design was sought from the ethics committee of the University of Regensburg, Germany before commencing the experiment (ethical approval number: 17-819-101). For a detailed descriptive overview and clinical characteristics of the sample see **Table 8**. All participants received detailed information about objective, methods, duration and potential side effects of the study. Every participant gave written informed consent before the start of the study and received an appropriate expense allowance after completion of the experiment.

Table 8.
Sample characteristics.

N (female)	45 (14)			
Tinnitus side (left/ right/ bilateral)	(5/ 8/ 32)			
Tinnitus loudness fluctuation (yes/ no)	(24/ 21)			
Tinnitus maskability (yes/ no/ don't know)	(31/ 5/ 9)			
Musician (yes/ no)	(4/ 41)			
	M ± SD	**Md**	**Min**	**Max**
Age (years)	52.29 ± 11.81	55.00	23.00	69.00
Tinnitus duration (months)	111.04 ± 72.90	96.00	18.00	280.00
Tinnitus frequency (Hz)	6251.09 ± 2811.38	5887.00	1020.00	15524.00
Tinnitus loudness (dB SPL)	51.38 ± 16.05	50.00	27.00	85.00
Hearing loss left (dB)	17.26 ± 13.61	14.69	-5.72	55.00
Hearing loss right (dB)	17.48 ± 11.52	17.43	-8.71	45.87
LDL left (dB) (25 missing values)	86.25 ± 3.21	85.50	81.00	90.00
LDL right (dB) (28 missing values)	85.06 ± 3.96	87.00	78.00	90.00
Minimum masking level (dB)	63.82 ± 14.60	60.00	37.00	90.00
Sensation Level (dB)	47.58 ± 17.49	45.00	21.00	86.00
TQ total score (0-84)	40.73 ± 15.70	40.00	17.00	71.00
THI total score (0-100)	35.91 ± 21.38	34.00	4.00	80.00
VAS awareness (%)	64.62 ± 29.62	70.00	8.00	100.00
VAS loudness (%)	61.11 ± 24.19	65.00	15.00	100.00
VAS bothersome (%)	38.20 ± 29.29	30.00	.00	100.00
GUF total score (0-45)	10.73 ± 6.45	10.00	.00	23.00

M = mean; SD = standard deviation; Md = median; Min = minimum; Max = maximum; LDL = Loudness Discomfort Level (missings in LDL are due to values over 90 dB); TQ = Tinnitus Questionnaire; THI = Tinnitus Handicap Inventory; VAS = Visual Analog Scale; GUF = Questionnaire on Hypersensitivity to Sound.

Psychometry

Prior to the start of the experiment, participants were requested to answer a set of questionnaires compiled of German versions of the Tinnitus Handicap Inventory (THI) (Kleinjung et al., 2007a; Newman et al., 1996), the Tinnitus Questionnaire (TQ) (Goebel and Hiller, 1994; Hallam et al., 1988), the Tinnitus Sample Case History Questionnaire (TSCHQ) (Langguth et al., 2007), visual analog scales (VAS, %) for tinnitus awareness, loudness and bothersome, as well as the Questionnaire on Hypersensitivity to Sound (GUF) (Bläsing et al., 2010) (participants with a score of > 23, which constitutes a very severe impairment, were excluded from our analysis). The survey was performed with SoSci Survey (Leiner, 2016).

Audiometry

Participants hearing thresholds were examined with the toolbox MultiThreshold (University of Essex, United Kingdom) using the implemented paradigm absolute threshold (absThreshold) in Matlab (Matlab R2017a; Mathworks, USA). This paradigm is an implementation of the two-alternatives forced-choice threshold estimation algorithm by Green (1993). Sine tones (0.5 seconds) were used to test participants hearing level for frequencies from 250 up to 8000 Hz on an octave scale for each ear separately. Starting loudness level was 30 dB SPL, which was increased by 10 dB steps until the participants were able to perceive the sound. The loudness level was raised by 2 dB steps between trials.

ER-2 Insert Earphones (Etymotic Research Inc., USA) together with an external soundcard (RME Fireface UCX; Audio AG, Germany) were used for hearing assessment, subsequent matching of the ITF, definition of the sensation level (SL), minimum masking level (MML) (compare section tinnitometry) as well as the proper auditory stimulation.

Tinnitometry

Individual tinnitus pitch matching was carried out using a Method of Adjustment approach modified from Henry et al. (2013) and Roberts et al. (2008) and implemented in a custom software tool (MAX 7; Cycling'74, USA). A custom-built hardware controller was used comprising a Teensy 3.2 USB-based micro-controller (PJRC, USA) and industrial-grade rotating knobs, switches and motor faders. Detailed information about the used tinnitus matching procedure is described in Neff et al. (2019). The starting frequency was defined as one frequency group below the frequency with the highest HL and a start loudness of 10 dB above the particular hearing threshold. Participants tried to match their tinnitus four times as

good as possible and rated the accordance of the matched sound with their perceived tinnitus on a 1 – 10 scale (1 = no accordance; 10 = perfect accordance) after each attempt.
The tinnitus matching trial with the highest rating was subsequently defined as the participants ITF. If participants rated different matching attempts similarly, the frequency closest to the mean frequency of the four attempts was chosen. The ITF was then used for the evaluation of further audiometric parameters. Similarly, the MML was defined by increasing the loudness of WN to the point of complete tinnitus masking. Assessment of the loudness discomfort level (LDL) of participants ITF was executed with the discomfort paradigm of the MultiThreshold toolbox with Sennheiser HDA 2000 headphones (Sennheiser, Germany).

Acoustic stimulation

Three different types of noise stimuli with a duration of three minutes each were created in Matlab (Matlab R2017a; Mathworks, USA) with an intensity of 65 dB SL (defined as the loudness level of participants first-time tinnitus pitch perception; maximum loudness of 85 dB SPL) for acoustic stimulation. For this purpose a genuine WN was used to produce individualized noise stimuli through the implementation of bandpass (IBP) and bandstop (IBS) filters with one octave width around the ITF (Pantev et al., 2012). Each stimuli was composed of a 1000 ms linear fade-in and fade-out phase and underwent a root-mean-square correction to balance levels between stimuli.
Diotic acoustic stimulation was performed at a maximum loudness of 85 dB SPL and each stimuli was presented only once. The presentation sequence of the stimuli was randomized. Before and after the presentation of each stimuli (3 minutes), participants were requested to sit quietly, focus on a white fixation cross on a black screen and avoid extensive eye-blinks and movements while their brain activity was recorded via EEG for three minutes respectively (compare section electrophysiological data acquisition and analysis).
After the presentation of each noise stimulus, patients had to rate the loudness of their tinnitus at seven different time points (0 sec, 30 sec, 60 sec, 90 sec, 120 sec, 150 sec and 180 sec after stimulation offset) on a customized keyboard strip (X-Key-Stick-16-USB, XK-0981-UCK16-R; P.I. Engineering, USA) with a numeric rating scale from 0% to 110%, whereas 100% signified no tinnitus loudness changes, 0% a total absence of tinnitus and 110% a tinnitus loudness increase by 10%. For an illustration of the acoustic stimulation procedure please see **Figure 5**. The whole experimental stimulation procedure was implemented with the Psychophysics Toolbox Version 3 (Brainard, 1997; Kleiner et al., 2007) in Matlab (Matlab R2017a; Mathworks, USA) and double-blinded.

At the end of the experiment, the three stimuli were again presented in a randomized order for 10 seconds each and participants were requested to rate the valence and the arousal of each stimuli via pictorial manikin scales (Bradley and Lang, 1994) on a 9-point Likert Scale, whereas the value 0 indicated a neutral stimulus evaluation (Valence: -4 unpleasant, 4 pleasant; Arousal: -4 relaxing, 4 upsetting).

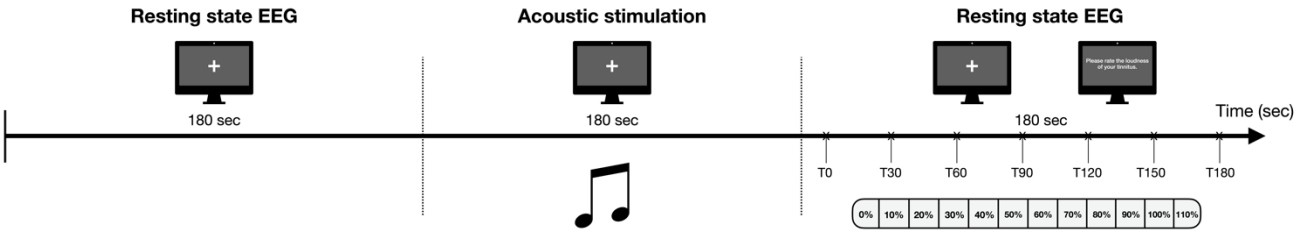

***Figure 5*. Acoustic stimulation procedure**.
Prior and post of acoustic stimulation (3 minutes), participants resting state brain activity was recorded via EEG (3 minutes). Participants were instructed accordingly and requested to focus on a white fixation cross on a black screen during the whole experiment. Following acoustic stimulation, participants were requested to rate the current loudness of their tinnitus (”Please rate the loudness of your tinnitus.”) at seven points in time (0, 30, 60, 90, 120, 150 and 180 seconds towards stimulation offset) on a numeric rating scale from 0% to 110% (0% - total absence of tinnitus; 100% - no tinnitus loudness changes; 110% - 10% tinnitus loudness increase). This acoustic stimulation procedure was repeated for each of the three used types of noise stimuli (white noise, individualized bandpass filtered white noise, individualized bandstop filtered white noise).

Behavioral analysis

Behavioral data was analyzed with the statistic software R (R version 3.4.2; R Foundation for Statistical Computing, Austria) and the packages "psych", "emmeans", "sjstats" and "lme4".

Linear mixed effect models were used to analyze tinnitus loudness ratings and stimuli evaluation (valence, arousal) separately. The following predictors were tested for the model fitting procedure of tinnitus loudness ratings: condition (stimuli, compare section acoustic stimulation, time (0 sec, 30 sec, 60 sec, 90 sec, 120 sec, 150 sec, 180 sec towards stimulation offset), tinnitus bilaterality (yes/ no), sex (male/ female), tinnitus duration and stimuli position in the auditory stimulation sequence. The predictors condition, gender and tinnitus duration were tested for the model fitting procedure of stimuli evaluation data.

Other potential predictors such as tinnitus loudness (dB), MML, SL or HL were not included in the model fitting procedure, since they were experimentally controlled e.g., by the creation of tailored stimuli. Participant (id) was considered as a random effect in all model fitting procedures.

In order to identify the model with the best fit for the data, the step function of the lme4 package was deployed. Thereby, a backward elimination of non significant predictors as well as a forward addition of significant predictors is conducted by comparing the models with

Likelihood Ratio Tests (Harrison et al., 2018). Marginal (variance of the predictors) and conditional (variance of predictor and random effect) R^2 were computed to provide the amount of the explained variance of the respective model (Nakagawa et al., 2017). For each final model, fixed effects were examined via Expected Mean Square Approach. Potential differences in tinnitus loudness and stimuli evaluation within predictors were analyzed with post-hoc Tukey-tests. Analysis of descriptive differences between HL and LDL between the left and right ear were tested by the means of two-sample t-tests. Normal distribution (Shapiro-Wilk-Test) and homoscedasticity (F-test) were examined and if violated, non-parametric testing with independent sample Mann-Whitney U-tests were conducted. To evaluate effect size of significant differences, Cohen's d was calculated. The level of statistical significance was set to $p \leq .05$ for all analyses.

Electrophysiological data acquisition and analysis

EEG recording

EEG data was recorded with a BrainAmp DC system, EasyCap electrode cap with 64 electrodes, and Brain Vision Recorder 1.20 software (Brain Products GmbH, Germany). The sampling rate was 500 Hz and electrodes were referenced to FCz during recording. Impedances were kept below 10 kΩ.

Preprocessing

Raw EEG data was preprocessed with a custom-built semi-automatic pipeline using the Fieldtrip toolbox (Oostenveld et al., 2011) in Matlab (Matlab R2017a; Mathworks, USA). EEG data was filtered between 0.5 Hz and 45 Hz with a 4th order Butterworth bandpass filter. Hereafter, an independent component analysis (ICA, fastICA http://research.ics.aalto.fi/ica/fastica/index.shtml) was used to identify and remove components with horizontal and vertical eye movement. Noisy or aberrant channels were interpolated using weighted neighbors. Neighboring channels were defined via a triangulation of 2D sensor position projection and channels identified for interpolation were replaced with the mean of neighboring sensors.

In a next step, average referencing was performed and the recording reference electrode FCz was added as a data channel. In order to control for noisy channels introduced by the rating procedure of the post stimulation conditions, posterior (Iz, TP9, TP10) as well as frontal channels (FPz, FP1, FP2, AF3, AF4, AF7, AF8) were discarded from subsequent analyses steps. Data was then segmented into 2 seconds segments. All segments during which participants

rated the loudness of their tinnitus were rejected. Additionally, one segment before and after the rating was excluded as well. Segments with remaining artifacts were rejected with combined automatic identification via a z-score (µV) threshold of -2/ +2 and visual inspection in a final step. Average number of valid segments was different (U = 1970.50, p = .001) between pre (M = 78.93, SD = 6.48) and post (M = 60.37, SD = 6.19) acoustic stimulation.

EEG analysis

Power analysis – whole group

Frequency power spectra of pre and post auditory stimulation datasets per subject and condition (compare section acoustic stimulation) were calculated using multitaper frequency transformation (mtmfft) and a hanning window with a spectral smoothing of 1 Hz. Next, grand averages were created for pre and post stimulation datasets per condition by computing power spectra averages across all valid segments and all subjects. Potential changes in EEG power spectra were analyzed with a 2 x 3 repeated measurement ANOVA and the within subject factors time (pre, post) and condition (WN, IBP, IBS), which was implemented in Fieldtrip. The main effects for time and condition were tested with paired two-sided t-tests via non-parametric cluster-based permutation tests with 10.000 iterations. In order to test for an interaction effect of time and condition, a dependent samples multivariate ANOVA was conducted using a non-parametric cluster-based permutation test with 10.000 iterations as well. We were primary interested in an interaction effect of time and condition.

In case of a significant time x condition interaction, effects were followed up using post-hoc contrasts. Pre vs. post contrast per condition were analyzed with dependent samples t-tests, whereas potential differences in stimuli-induced power spectra changes from pre to post stimulation as well as post stimulation differences (inter-stimulus contrasts), were contrasted via independent samples t-tests using non-parametric cluster-based permutation test as described above.

Additionally, Pearson correlations between post stimulation power spectra and pre-post power spectra differences with averaged tinnitus loudness ratings (over all 7 time points) as well as directly after stimulation offset (T0) were computed via cluster-based permutation tests. Significance level was set to $p \leq .05$ for all EEG analyses and $p < 0.1$ was defined as a statistical trend. Significant clusters were defined as a minimum of two significant neighboring channels for all analysis. For the purpose of interpretation, EEG frequency bands were defined as follows: delta 1 – 4 Hz, theta 5 – 7 Hz, alpha 8 – 12 Hz, beta 13 – 29 Hz, gamma 30 – 45 Hz.

Power analysis – responder

Furthermore, we compared frequency power spectra of participants who exhibited RI with those who did not experience RI after auditory stimulation. For this purpose RI was defined as ≤ 50% of tinnitus loudness directly after stimulation offset resulting in a subset of n = 12 further indicated as responders. Within this subgroup of responders, n = 5 participants each, responded to a stimulation with WN or IBP, whereas only n = 2 participants reported RI after a stimulation with IBS. A second subgroup of participants without RI (non-responders) were matched to responders according to the following criteria: gender; mean HL; age and absence of RI (tinnitus loudness of ≥ 100% after stimulation offset) in the same stimulus type as matched patient exhibited RI in the responders group. Sample characteristics for both subgroups can be seen from **Table 9**.

Associations of categorical variables with stimulation response (responder or non-responder) were analyzed with χ^2-tests or Fisher's exact tests if cell frequencies were below 5. Differences in numerical variables between the two subgroups were analyzed by two-sample t-tests. In case of violated statistical assumptions, Mann-Whitney U-tests were performed. Significance levels were set to $p \leq .05$ and a statistical trend was defined as < 0.1.

Power spectra for pre and post auditory stimulation EEG datasets were averaged over all subjects within the respective subgroup (responders and non-responders). Analyses were conducted using normalized EEG datasets by dividing power spectra for each single frequency through the mean power of the entire frequency spectrum. Illustrated power spectra per frequency were transformed according to 10 * log10(x).

EEG power spectra were analyzed with a 2 x 2 repeated measures ANOVA and the factors time (pre, post) and group (responders, non-responders). The main effects for time and group were evaluated with dependent sample respectively independent sample t-tests according to the same approach as already described in the power analysis section for the whole group. Likewise, a potential interaction effect of time and group was analyzed with an independent samples t-test. In the case of a significant interaction effect, post-hoc dependent samples t-tests for pre vs. post within subgroup contrast and independent samples t-tests for between subgroup contrast (responders vs. non-responders) separated for pre and post stimulation measurements are conducted. Regardless of an observed interaction effect, an exploratory contrast of post stimulation power spectra differences between responders and non-responders is performed.

Equal to the whole group analysis, Pearson correlations were calculated with cluster-based permutation tests for post stimulation power spectra and pre-post power spectra differences with averaged tinnitus loudness ratings or rather directly after stimulation offset (T0).

Additionally, a correlation of post stimulation power spectra and pre-post power spectra differences with tinnitus loudness rated via VAS (%) was computed. In order to explore differences in cortical alpha variability between responders and non-responders a coefficient of variance was calculated by dividing the standard deviation of the alpha frequency power (8 – 12 Hz) by its mean power.

Source space analysis

Source localization of frequency data was performed using a standard boundary element headmodel (Oostenveld et al., 2003) and the dynamic imaging of coherent sources algorithm optimized for EEG frequency data (Dynamical Imaging of Coherent Sources, (Gross et al., 2001). Inter-subgroup source contrasts (responders vs. non-responders; responders vs. non-responders post stimulation) of peak frequencies received from sensor-level cluster analysis (maximum value) were analyzed via non-parametric cluster-based permutation tests with 10.000 iterations using normalized EEG datasets. Normalization procedure was identical to the sensor level analysis.

Results

Sample characteristics

Table 8 summarizes the descriptive statistics and tinnitus-related questionnaire scores of the present sample. In the majority of participants, tinnitus was perceived bilaterally (n = 32) and featured loudness fluctuations (n = 24). The possibility to mask their perceived tinnitus was reported by n = 31 participants. Moreover, n = 4 participants claimed to be musicians and the average duration of tinnitus perception was 111.04 months (SD = 72.90).

Stimulation with either WN, IBP and IBS resulted in n = 12 responders, who showed RI with at least one stimulus type. A weak association of stimulation response (responders or non-responders) and tinnitus maskability (yes, no, don´t know) was found with the group of responders exhibiting no participant who reported an absence of tinnitus maskability (cf. **Table 9**).

Table 9.

Sample characteristics - responders vs. non-responders.

	Responders				Non-responders					p
N (female)	11 (1)				11 (1)					
Tinnitus side (left/ right/ bilateral)	(0/ 5/ 7)				(3/ 2/ 7)					.189
Tinnitus loudness fluctuation (yes/ no)	(7/ 5)				(6/ 6)					.682
Tinnitus maskability (yes/ no/ don't know)	(7/ 0/ 5)				(7/ 2/ 3)					.063
Musician (yes/ no)	(3/ 9)				(1/ 11)					.590
	M ± SD	**Md**	**Min**	**Max**	**M ± SD**	**Md**	**Min**	**Max**	**t (df)/ U**	**p**
Age (years)	54.17 ± 12.14	48.00	31.00	66.00	54.38 ± 6.98	52.00	49.00	69.00	83.00	.540
Tinnitus duration (months)	77.00 ± 69.48	66.00	24.00	280.00	159.58 ± 75.91	165.00	51.00	252.00	**26.00**	**.008**
Tinnitus frequency (Hz)	5271.58 ± 1985.77	5878.00	2250.00	9488.00	6661.75 ± 2451.11	6842.00	3226.00	10136.00	$-1.53_{(21.30)}$	.142
Tinnitus loudness (dB SPL)	53.25 ± 14.78	54.00	32.00	72.00	53.92 ± 12.30	54.00	35.00	74.00	$-.12_{(21.30)}$	.905
Hearing loss left (dB)	19.75 ± 14.70	17.00	6.47	46.64	20.61 ± 11.17	18.20	6.62	38.78	65.50	.729
Hearing loss right (dB)	19.89 ± 7.89	21.43	7.37	30.52	19.95 ± 11.25	21.20	5.88	38.31	$-.01_{(19.83)}$	.988
LDL left (dB) (5 missing values/ 11 missing values)	85.71 ± 2.93	84.00	84.00	90.00	90.00	-	-	-	1.00	.302
LDL right (dB) (7 missing values/ 8 missing values)	83.04 ± 6.15	81.00	78.00	90.00	86.25 ± 3.77	87.00	81.00	90.00	$-.85_{(6.68)}$	.422
Minimum masking level (dB)	56.33 ± 13.15	53.00	44.00	79.00	72.92 ± 15.19	74.50	54.00	90.00	**28.00**	**.012**
Sensation Level (dB)	46.00 ± 15.85	46.50	24.00	66.00	52.58 ± 8.84	53.00	39.00	70.00	$-1.26_{(17.24)}$	.225
TQ total score (0-84)	28.00 ± 10.87	23.50	19.00	55.00	49.00 ± 15.20	43.50	30.00	71.00	**14.50**	**<.001**
THI total score (0-100)	22.83 ± 16.37	14.00	4.00	52.00	48.00 ± 23.34	40.00	14.00	76.00	$\mathbf{-3.30_{(19.71)}}$	**.004**
VAS awareness (%)	50.00 ± 28.92	30.00	20.00	90.00	80.83 ± 25.75	100.00	30.00	100.00	**26.50**	**.008**
VAS loudness (%)	48.75 ± 16.25	52.50	30.00	75.00	73.33 ± 16.65	80.00	50.00	100.00	**22.50**	**.004**
VAS bothersome (%)	21.33 ± 21.98	20.00	.00	75.00	45.83 ± 29.99	45.00	10.00	100.00	**34.00**	**.029**
GUF total score (0-45)	6.00 ± 5.48	5.00	.00	20.00	12.17 ± 5.37	11.50	1.00	20.00	**28.50**	**.012**

M = mean; SD = standard deviation; Md = median; Min = minimum; Max = maximum; df = degrees of freedom; LDL = Loudness Discomfort Level (missings in LDL are due to values over 90 dB); TQ = Tinnitus Questionnaire; THI = Tinnitus Handicap Inventory; VAS = Visual Analog Scale; GUF = Questionnaire on Hypersensitivity to Sound.

Statistical testing for differences between the subgroups of responders and non-responders revealed differences in terms of tinnitus duration, MML and questionnaire data with the group of responders showing shorter tinnitus duration (U = 26.00, p = .008, d = 1.135), lower MML (U = 28.00, p = .012. d = 1.168) as well as lower sum scores in TQ (U = 14.50, p < .001, d = 1.159), THI ($t_{(19.71)}$ = -3.30, p = .004, d = 1.249) and GUF (U = 28.50, p = .012, d = 1.137). Likewise, responders reported lower values in subjective measurements of tinnitus awareness (U = 26.50, p = .008, d = 1.126), loudness (U = 22.50, p = .004, d = 1.494) and bothersome (U = 34.00, p =.029, d = .931) as indicated by VAS (in %). Detailed sample characteristics and statistical comparisons for the two subgroups are shown in **Table 9**.

Audiometry and tinnitometry

Results from audiometric assessment and tinnitus matching are outlined in **Table 8** as well as illustrated in **Figure S2**. The investigated sample featured a mean tinnitus frequency of 6251.09 Hz (SD = 2811.38), whereas the average tinnitus loudness was 51.38 dB SPL (SD = 16.05). Initial perception of the individual tinnitus pitch (SL) appeared at a mean volume level of 47.58 dB (SD = 17.49). Mann-Whitney U-tests found no differences with respect to HL (U = 941.50, p = .569) and LDL (U = 199.50, p = .361) between the left and the right ear.

Acoustic stimulation

Table S5 lists the descriptive statistics for tinnitus loudness ratings for each stimuli on average as well as time point T0. Tinnitus suppression time curves, including all seven time points, are illustrated in **Figure 6** for each stimuli. Model fitting procedure of behavioural data was able to identify the following model with the best fit for the data: *response ~ condition + (1|id)*. **Table S6** lists detailed results of the model fitting proceeding. A significant effect of condition was observed (cf. **Table S7**). Succeeding post-hoc contrasts found differences between stimulus WN vs. IBS, as well as IBP vs. IBS (cf. **Table 10**). A potential confounding caused by the position of the stimuli in the acoustic stimulation sequence could be excluded, since position did not appear as a significant predictor in the final model.

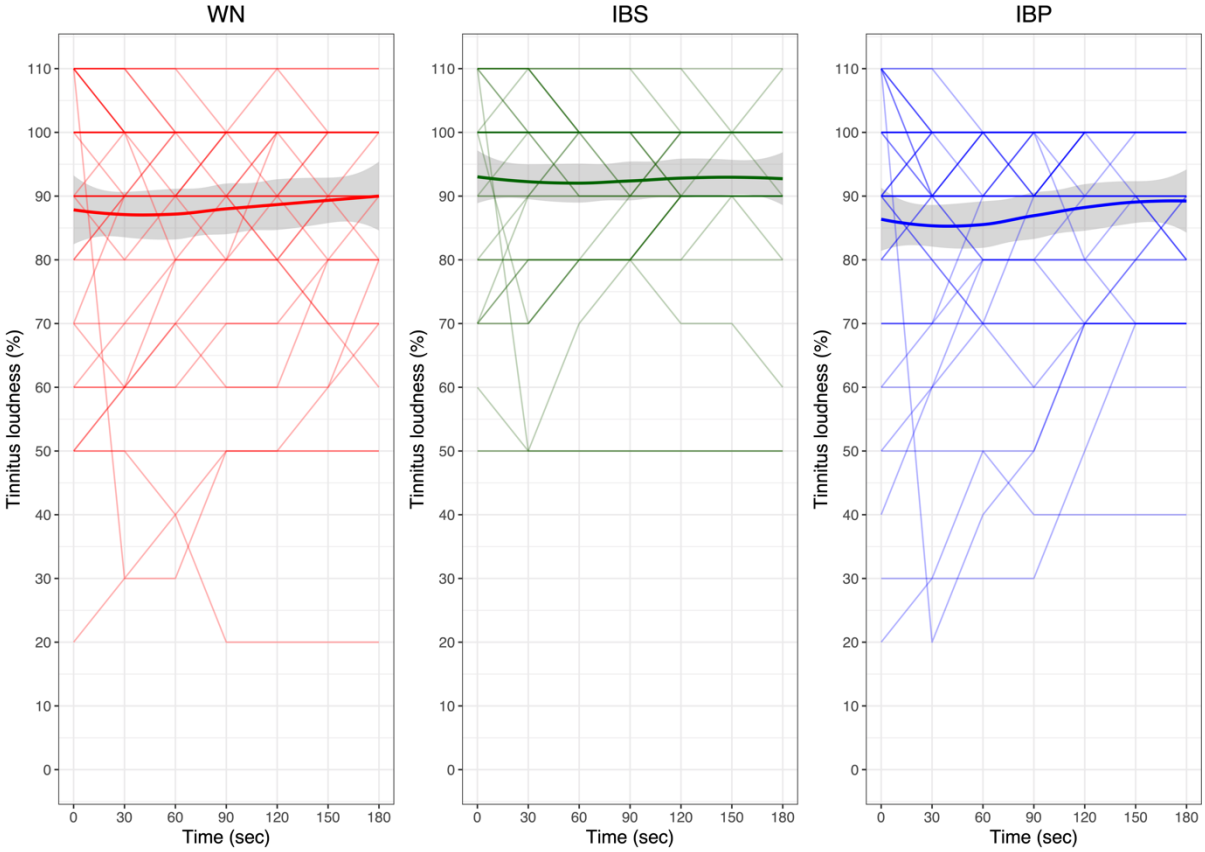

***Figure 6*. Tinnitus loudness time curve per condition.**
WN = white noise; IBP = individualized bandpass filtered white noise; IBS = individualized bandstop filtered white noise. Tinnitus loudness ratings are illustrated on a single participant level for all rating timepoints separated for each stimuli. Thick lines show the mean tinnitus loudness (%) per stimulus, standard deviations are illustrated as grey ribbons.

Table 10.
Post-hoc tukey contrasts for condition.

Contrast	Estimate	t	p	d
Total sample				
WN – IBP	1.05	1.20	.451	.057
WN – IBS	**-4.32**	**-4.96**	**<.001**	**.251**
IBP – IBS	**5.37**	**-6.17**	**<.001**	**.328**

WN = white noise; IBP = individualized bandpass filtered white noise; IBS = individualized bandstop filtered white noise; degrees of freedom = 902.00; standard error = .87.

Stimulus evaluation

Stimulus evaluation outcomes in terms of valence and arousal can be seen from **Table S8** and **Figure S3**. Model *response ~ condition + (1|id)* was identified to have the best fit for the valence data with condition as a significant fixed effect (cf. **Tables S9** and **S10**). Post-hoc tests were able to reveal differences for valence evaluations of stimuli WN vs. IBS and also IBP vs. IBS as can be seen from **Table S11**. Subsequent model was identified by our model fitting approach for arousal data: *response ~ condition + gender + (1|id)* (cf. **Table S9**). Fixed effect testing revealed significant effects for condition and gender (cf. **Table S10**). Post-hoc analysis showed differences between stimuli IBP and IBS as well as male and female participants (cf. **Table S11**).

Electrophysiology

Results of whole sample EEG power spectra analysis are outlined in **Table 11**. A significant main effect of time was observed, indicating higher spectral power for 1 – 7 Hz and 26 – 45 Hz plus lower spectral power for 7 – 28 Hz after auditory stimulation. Further, a significant interaction of condition and time was found in the frequency spectra 1 – 7 Hz and 36 – 45 Hz. Succeeding post-hoc contrasts revealed higher power in lower frequencies towards stimulation across all stimuli (WN: 1 – 7 Hz; IBP: 1 – 6 Hz; IBS: 1 – 6 Hz) as well as higher gamma activity after a stimulation with IBP (32 – 45 Hz) and IBS (37 – 45 Hz). A power decrease following IBS stimulation was found for the frequency cluster 11 – 19 Hz. In addition, statistical trends towards power reductions in the frequency clusters 10 – 12 Hz and 14 – 19 Hz were observed for pre-post comparisons of stimulus WN. Differences between the applied types of stimuli with respect to pre-post power spectra changes or post stimulation power spectra were not detected. Electrodes within frequency clusters as outlined in **Table 11** can be found in the supplemental material in **Table S12** grouped by brain areas.

No correlations were found on the cluster level for post stimulation EEG power or pre-post power spectra changes with averaged tinnitus loudness ratings or rather tinnitus loudness ratings immediately after stimulation end (T0) for any of the used stimuli.

Table 12 provides the results obtained from the responder EEG power spectra analysis (compare section EEG analysis). A significant main effect of time was observed, indicating a power reduction from pre to post stimulation in the frequency cluster 6 – 32 Hz for responders as well as non-responders.

Table 11.
Electrophysiology - results of cluster-based permutation test for the total sample analysis.

	Frequency (Hz)	Cluster statistic (df)	p	Peak frequency (Hz)	Peak electrode	Max. statistic
Time						
Positive cluster	1 – 7	$t_{(134)} = 1047.88$	<.001	4	PO8	7.68
Positive cluster	26 – 45	$t_{(134)} = 893.13$	<.001	41	POz	4.89
Negative cluster	7 – 28	$t_{(134)} = -1150.64$	<.001	12	T8	-5.33
Condition x Time						
Positive cluster	1 – 7	$F_{(5,40)} = 3437.77$	.002	4	PO8	51.28
Positive cluster	36 – 45	$F_{(5,40)} = 2783.52$	.002	42	F6	34.09
Post-hoc - pre vs. post stimulation per stimulus						
Positive cluster						
WN	1 – 7	$t_{(44)} = 482.28$	.006	5	O1	4.81
IBP	1 – 6	$t_{(44)} = 696.17$	.002	3	O1	5.90
IBP	32 – 45	$t_{(44)} = 460.98$	.007	41	F3	4.44
IBS	1 – 6	$t_{(44)} = 398.13$	.006	3	O2	4.20
IBS	37 – 45	$t_{(44)} = 199.09$	.026	45	P2	3.54
Negative cluster						
WN	10 – 12	$t_{(44)} = -132.92$	.058	11	T8	-4.24
WN	14 – 19	$t_{(44)} = -123.90$	.064	19	C3	-3.95
IBS	11 – 19	$t_{(44)} = -242.31$	.016	13	T8	-4.20

WN = white noise; IBP = individualized bandpass filtered white noise; IBS = individualized bandstop filtered white noise; df = degrees of freedom; Max = maximum. Positive clusters indicate increased power spectra whereas negative clusters indicate decreased power spectra from pre to post stimulation, in the respective frequency ranges. Peak frequency (Hz) and peak electrode represent the particular frequency and electrode featuring the maximum value obtained from cluster statistics.

Table 12.

Electrophysiology - results of cluster-based permutation test for the responder analysis analysis.

	Frequency (Hz)	Cluster statistic (df)	p	Peak frequency (Hz)	Peak electrode	Max. statistic
Time						
Negative cluster	6 – 32	$t_{(11)} = -1539.00$	<.001	18	TP7	-6.77
Group						
Positive cluster	7 – 12	$t_{(22)} = 246.27$	.082	9	F4	4.35
Negative cluster	22 – 45	$t_{(22)} = -573.34$	.024	31	P5	-4.06
Exploratory post-hoc contrast - responders vs. non-responders post stimulation						
Positive cluster	5 – 17	$t_{(22)} = 549.39$	.035	9	F4	4.94

Df = degrees of freedom; Max = maximum. Positive clusters indicate increased power spectra, whereas negative clusters indicate decreased power spectra for responders compared to non-responders respectively from pre to post stimulation (effect of time) in the respective frequency ranges. Peak frequency (Hz) and peak electrode represent the particular frequency and electrode featuring the maximum value obtained from cluster statistics.

Likewise, a significant effect of group demonstrates lower power in higher frequency ranges (22 – 45 Hz; $t_{(max)}$ = -4.06, over electrode P5 at 31 Hz; cf. **Figure 7 A** and **B**) as well as a statistical trend towards higher power in the alpha frequency range (7 – 12 Hz; $t_{(max)}$ = 4.35, over electrode F4 at 9 Hz; cf. **Figure 7 A** and **B**) for the subgroup of responders. There was no significant interaction of time and group. Electrodes within frequency cluster presented in **Table 12** can be found in **Table S13** in the supplemental material. Coefficient of variance calculation exclusively for the alpha frequency band (8 – 12 Hz) exposed a higher variation in frequency band power for the subgroup of responders (responders: 61.04%; non-responders: 50.03%).

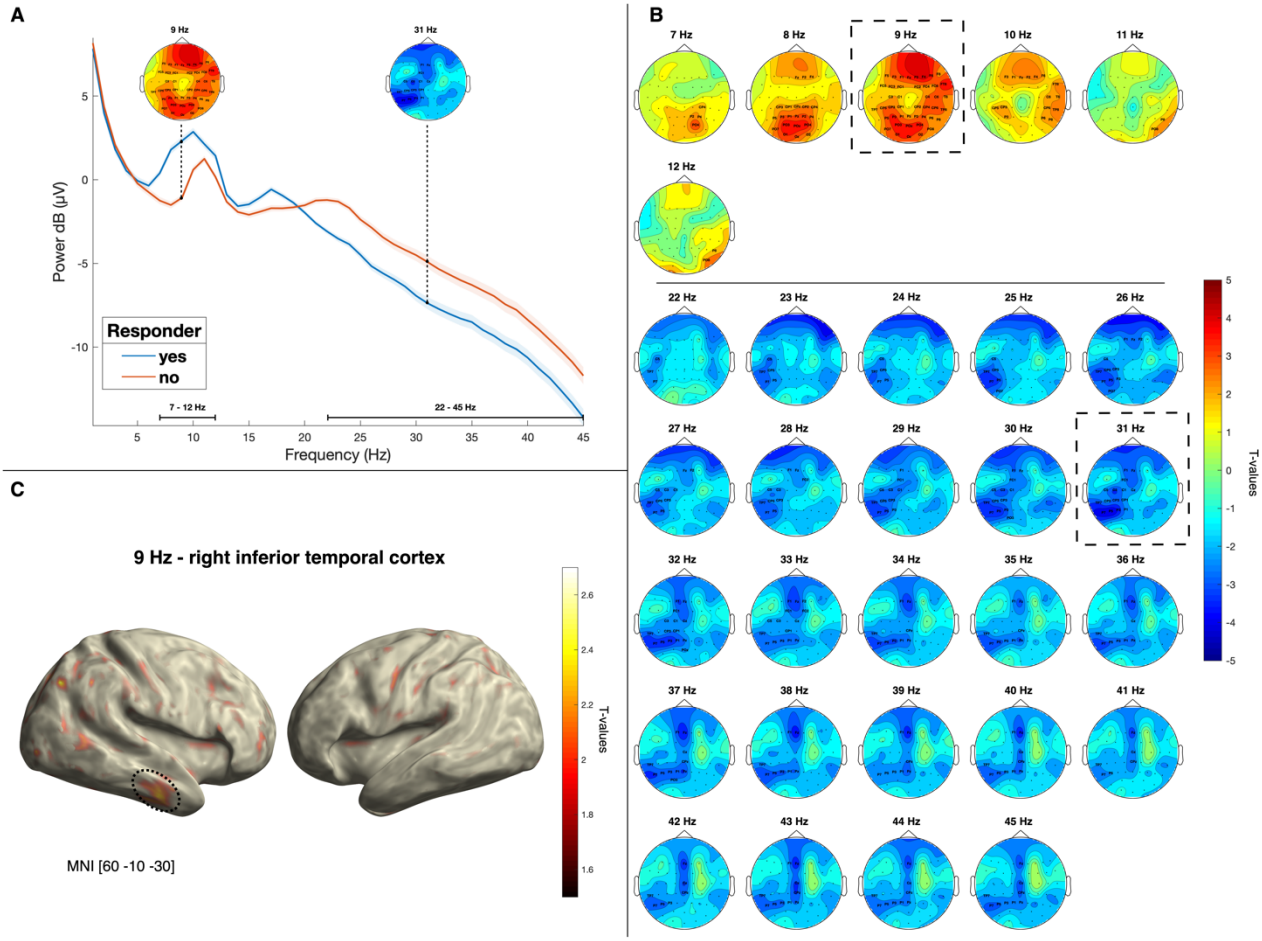

***Figure 7*. Responders vs. non-responders - contrast of power spectra at the sensor and source level**.
A: Power spectra differences for responders and non-responders for the frequencies 1 – 45 Hz. Significant positive cluster 5 – 17 Hz and negative cluster 22 – 45 Hz as well as the respective peak frequencies (9 Hz and 31 Hz) are highlighted. Grey ribbons represent the standard deviation for each subgroup. **B:** Cluster statistic results (t-values) of power spectra contrasts between responders and non-responders are presented as topographic plots per frequency for a positive cluster of 5 – 17 HZ and a negative cluster of 22 – 45 Hz. Significant cluster electrodes are accentuated in bold and labeled per frequency. Peak frequencies of 9 Hz and 31 Hz, representing the maximum values obtained from the cluster statistics, are highlighted with dashed line rectangles. **C:** Source localization of 9 Hz EEG power peaking in the right inferior temporal gyrus (BA 20).

Correlations of EEG power towards stimulation or pre-post power spectra changes on the cluster level with subjective tinnitus ratings for the group of responders showed no significant results for mean tinnitus loudness or tinnitus loudness at T0. Further no correlation with tinnitus loudness rated via VAS (%) was observed.

Subsequent exploratory analysis of post stimulation power spectra differences between responders and non-responders, exhibited increased activity in the frequency cluster 5 – 17 Hz in the subgroup of responders ($t_{(max)} = 4.94$, over electrode F4 at 9 Hz; cf. **Table 12** and **Figure 8 A** and **B**). Projecting peak frequencies of sensor-level power differences of responders and non-responders contrasts in source space exposed differences solely for 9 Hz ($t_{(cluster)} = 13.07$, $p = .004$) with maximum differences ($t_{(max)} = 2.70$) localized in the right inferior temporal gyrus (MNI: 60, -10, -30) shown in **Figure 7 C**). However, no difference at the peak frequency 31 Hz could be observed in source space. Source localization of the peak frequency received from sensor-level contrast between responders and non-responders post acoustic stimulation exhibited differences at the frequency of 9 Hz ($t_{(cluster)} = 31.95$, $p = .032$) localized in the right superior temporal gyrus (MNI: 40, -30, 10) presented in **Figure 8 C**.

Discussion

The main objective of the present study was to investigate the effect of different types of noise stimuli on short-term tinnitus suppression and corresponding electrophysiological brain activity. Moreover, we wanted to elucidate if electrophysiological changes are a function of tinnitus loudness ratings and if differential activation patterns arise from the different stimuli putatively triggering RI or lateral inhibition, respectively. Finally, we aimed at examining potential differences in ongoing brain activity between responders and non-responders. To the best of our knowledge, this presentation of notch- and bandpass-filtered WN sounds is novel in its application in tinnitus research. Similarly, we are the first group which elucidated neurophysiological differences between acoustic stimulation responders and non-responders. In the following, the results of our study are thus critically discussed in the light of current knowledge and with respect to future research outlook.

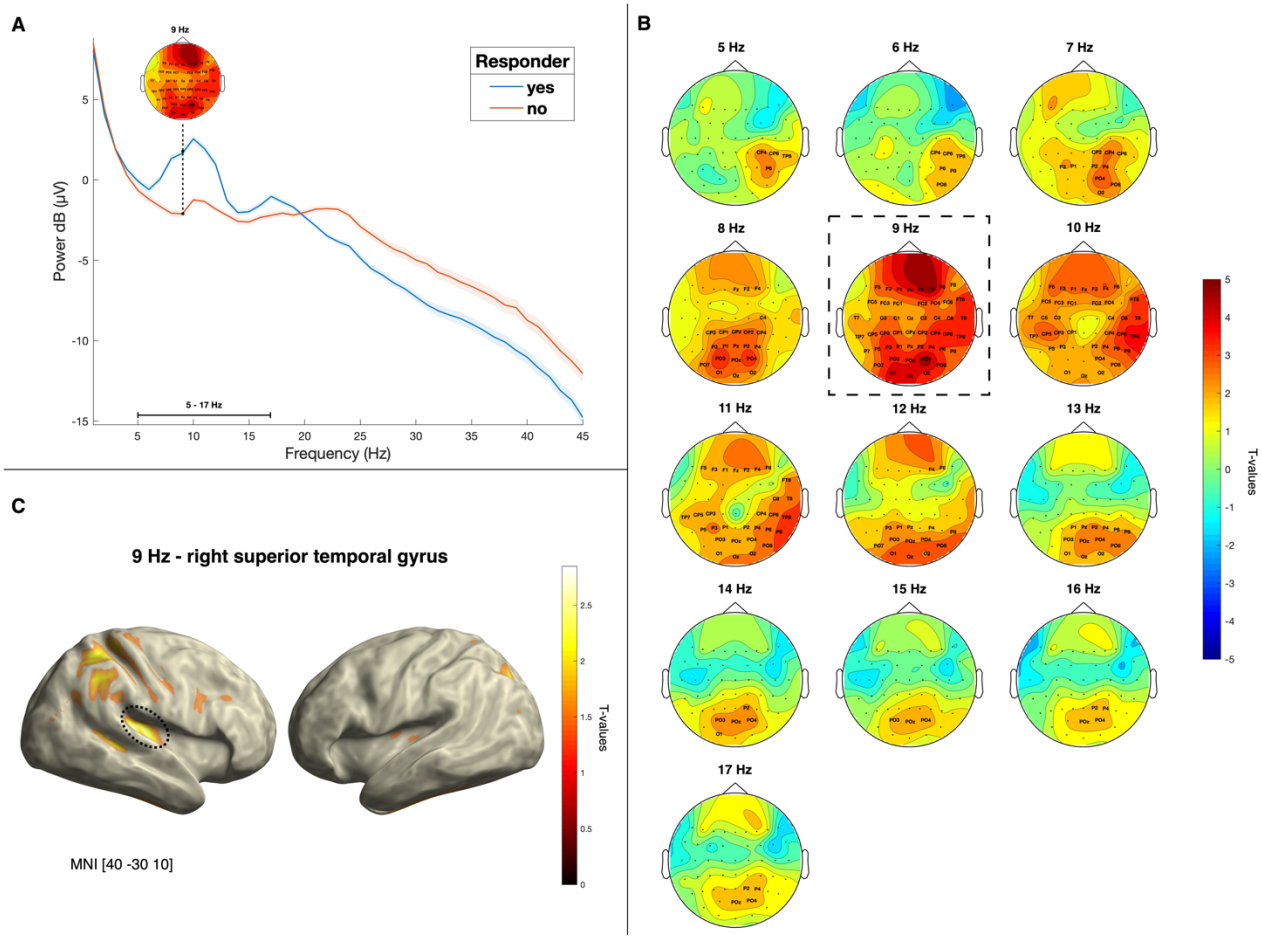

***Figure 8*. Responders vs. non-responders - post stimulation power spectra contrast at the sensor and source level**.

A: Power spectra differences for responders and non-responders for the frequencies 1 – 45 Hz. Significant positive cluster 5-17 Hz with the respective peak frequency of 9 Hz is highlighted. Grey ribbons represent the standard deviation for each subgroup. **B:** Results of cluster statistics (t-values) of power spectra contrasts between responders and non-responders following acoustic stimulation are presented as topographic plots per frequency for a positive cluster comprised of 5-17 Hz. Significant cluster electrodes are accentuated in bold and labeled per frequency. Peak frequency of 9 Hz is highlighted with a dashed line rectangle. **C:** Source localization of 9 Hz EEG power peaking in the right superior temporal gyrus (BA 41).

Behavioral results

The behavioral analyses demonstrate similar suppression patterns as past studies in this field with only a subset of the study population reporting a considerable tinnitus loudness reduction after acoustic stimulation. On a group level all of the used stimuli induced short-term tinnitus suppression. Contrary to our hypothesis IBS appeared to produce the fewest reduction in tinnitus loudness rating, whereas IBP resulted in the strongest suppression pattern. A potential explanation for this difference might derive from the ability of IBP/ WN in stimulating a broader range of frequencies around the ITF leading to a reduction of neural response gain and tinnitus-related hyperactivity and as a result facilitating short-term tinnitus suppression (cf.

Schaette et al., (2010)), whereas suppressing effects of IBS via lateral inhibition might only appear after long-term application. However, it is also possible that so called feed-forward inhibition is responsible for the superiority of stimuli containing signal in frequency ranges affected by hearing loss (cf. Roberts (2007); Roberts et al. (2010)). These explanations remain highly speculative and currently we are not able to provide a suitable explanation for these observed differences. Interestingly, stimulus IBP was evaluated with the lowest tolerability as indicated by the highest arousal and lowest valence ratings. This finding is contrary to one of our previous experiments which reports low arousal and high valence ratings for IBP (Schoisswohl et al., 2019b).

Generally, about 50 to 90% of the studied individuals report some level of tinnitus suppression after acoustic stimulation (Fournier et al., 2018; Kahlbrock and Weisz, 2008; Neff et al., 2017; Schoisswohl et al., 2019; Sedley et al., 2012). Given the skewed distribution of RI responses on the group level in previous and this study as well as the need for a reliable threshold for strong tinnitus suppression, we opted to define a reduction in tinnitus of 50% after acoustic stimulation as the threshold for the responder classification akin to Kahlbrock and Weisz (2008). Applying this threshold, we can report an absolute number of 12 responders (with any stimulus type) out of 45 participants (26.67% responder rate) which is comparable to relative numbers reported by Kahlbrock and Weisz (2008) (26% responder rate), but below the quantity of responders reported by King et al. (2020) (56.67% responder rate; the threshold for RI in this study is currently unknown due to publication status).

Electrophysiology

Since only a handful of studies evaluated neural activity during RI, no specific hypotheses were generated about oscillatory changes from pre to post stimulation. In light of past neurophysiological research and the assumptions that tinnitus is accompanied by abnormal delta, alpha and gamma activity (Adjamian et al., 2012; Ashton et al., 2007; Balkenhol et al., 2013; van der Loo et al., 2009; Moazami-Goudarzi et al., 2010; Weisz et al., 2007a, 2005) as well as a putative brief inversion of altered spontaneous brain activity during RI (Kahlbrock and Weisz, 2008), it can be supposed that observed group-level changes in tinnitus loudness (RI) are also reflected in electrophysiological measures. Namely, a reduction in delta and gamma and an increase in alpha power spectra from pre to post stimulation is to be expected given these assumptions.

Whole group analysis

Analysis of whole group pre-post stimulation changes in ongoing brain activity revealed increases in the delta, theta and gamma frequency range as well as decreases in alpha and beta frequency bands. This increase in low frequency activity is in direct contrast to past observations, which report a reduction of delta and theta power spectra during RI in accordance with the current neurophysiological models for tinnitus (Kahlbrock and Weisz, 2008; Sedley et al., 2015, 2012). In contrast, an earlier study using neuromagnetic measures in a single subject during short-term tinnitus suppression likewise reports an enhancement of low frequency activity (Kristeva-Feige et al., 1995). Gamma band activity was suggested to represent a spontaneous brain activity pattern related to the actual tinnitus perception (Weisz et al., 2007a), therefore it is assumed that during a potential suppression of tinnitus after acoustic stimulation, activity in the gamma band will be suppressed.

The current findings revealed an increase in gamma power after auditory stimulation, similar to findings from King et al. (2020) or Sedley et al. (2015, 2012), who observed an increase in gamma band activity during RI. Consistent with the current literature, we observed a decrease in alpha frequency band power from pre to post stimulation (Kahlbrock and Weisz, 2008; Sedley et al., 2015). However, a recent study was able to demonstrate an increase in alpha frequency band power during RI in accordance with the given neurophysiological models in tinnitus (King et al., 2020).

No relationship of pre-post power spectra changes, neither with tinnitus loudness ratings averaged over all time points nor directly after stimulation offset was observed in our data.

Past neurophysiological research was not able to produce consistent findings in terms of correlations with behavioral measures of tinnitus respectively RI (e.g., intensity, loudness).

Besides observed positive correlations of low and high frequency activity (Balkenhol et al., 2013; van der Loo et al., 2009; Sedley et al., 2012) or alpha activity with tinnitus intensity (Meyer et al., 2014; Sedley et al., 2015), the current findings are in accordance with other studies which report an absence of any relationship (Adjamian et al., 2012; Kahlbrock and Weisz, 2008; Pierzycki et al., 2016).

In consideration of missing correlations as well as power spectra changes in conflict with current neurophysiological models for tinnitus, we suggest that the present findings do not indicate oscillatory patterns related to tinnitus loudness suppression, rather constitute a tinnitus-unspecific neurophysiological reaction to an external acoustic stimulus. Oscillatory activity in the alpha frequency range is supposed to be relevant for inhibitory processes of the brain (Klimesch et al., 2007) thus a sound stimulation exceeding the individual tinnitus loudness level

produces excitation and consequently alpha decreases. It has already been shown, that spontaneous activity in the alpha (6 – 12 Hz) and beta (~ 20 Hz) frequency bands desynchronize after sound stimulation (for an overview see Weisz et al. (2011)). Likewise, gamma band activity (30 – 45 Hz; 80 – 100 Hz), which is associated with cortical activation like attention or perception, was observed to be enhanced after the presentation of sound stimuli (Crone et al., 2001; Joliot et al., 1994) comparable to the present and recent findings (King et al., 2020).
In order to distinguish spontaneous brain activity related to tinnitus suppression from tinnitus-unspecific neurophysiological consequences to a sound stimulation, future research should not only compare acoustic stimulation responders and non-responders (RI vs. absence of RI) but also strive for a comparison with healthy control groups.

Responder analysis

Another objective of this study was to compare acoustic stimulation responders with non-responders, in order to point out potential differences in regards to ongoing brain activity.
To the best of our knowledge this is the first study, which compares oscillatory activity of acoustic stimulation responders and non-responders. Interestingly, we observed reduced gamma band activity and a trend for enhanced alpha activity (peak frequency of 9 Hz localized in the right inferior temporal gyrus; BA 20) for the group of responders in contrast to non-responders. This result may corroborate the premise that gamma might be related to tinnitus perception (Ashton et al., 2007; De Ridder et al., 2015a; van der Loo et al., 2009; Weisz et al., 2007b). Given the fact, that responders generally reported their perceived tinnitus loudness level lower than non-responders, the question arises if the perceived tinnitus loudness rated via VAS can be associated with ongoing brain activity e.g., lower tinnitus loudness related to reduced gamma power or enhanced alpha. Yet, a respective correlation analysis failed to show an association. As already shown by Schlee et al. (2014), tinnitus sufferers exhibited a blunted alpha peak and more importantly reduced alpha variability (8 – 10 Hz). This finding could be reflected by our data in a similar way as non-responders had a lower alpha peak and lower alpha variability (8 – 12 Hz). In further support for this argumentation, the data of the former study as well as our present findings show longer tinnitus duration for subjects with reduced alpha power, whereas we assume that these insights from case-control contrasts can be applied to the responder analysis at hand.
The observed reduction in gamma power may be interpreted along similar veins as the findings in alpha power by applying insights from case-control studies. Responders with a less chronified and intense tinnitus in our study are thus comparable to healthy controls in some

case-control designs with reported lower gamma power values (Ashton et al., 2007; Vanneste et al., 2011c). In further analogy, our findings of diminished gamma band activity together with a decrease in tinnitus loudness for the subgroup of responders can be linked to observations of past studies, namely a positive correlation of gamma with tinnitus loudness (Balkenhol et al., 2013; De Ridder et al., 2015a; van der Loo et al., 2009). We theorize that this trend for blunted alpha as well as lower gamma activity may be indicative of a trait as a consequence of tinnitus chronification. A related observation was made by Neff et al. (2019) where active listening to tinnitus and consequential increase in tinnitus intensity did not lead to any neural alterations, which fits the reasoning about a trait-like neural representation of chronified tinnitus. However, it is also possible that this pattern of reduced gamma and enhanced alpha activity represent a genuine neural trait related to acoustic stimulation response more specifically the possibility to induce RI in tinnitus sufferers.

Our exploratory analysis of post acoustic stimulation contrasts revealed higher spectral power in the theta, alpha and beta frequency range with a peak in the alpha band (9 Hz) localized in the right superior temporal gyrus (BA 41) in acoustic stimulation responders. This increased alpha in auditory fields is in line with our hypothesis of a brief inversion of altered oscillatory power during RI and is consistent with past research examining disparities between tinnitus and healthy controls (compare introduction). Notably, this supports our assumptions about responders and related trait-like neural signatures of tinnitus in that it surmises that only responders can exhibit neural responses which are specific to RI induced by acoustic stimulation.

Finally, a lack of correlations between loudness ratings and ongoing brain activity in the present study does not allow for a conclusive interpretation with regards to tinnitus. Past studies examining correlates of tinnitus suppression and neural activity have been able to demonstrate a relationship of low and high frequency activity with tinnitus intensity (Sedley et al., 2015, 2012). Nevertheless Kahlbrock and Weisz (2008) were not able to demonstrate a correlation of tinnitus suppression and ongoing neural activity in agreement with the present findings. To further investigate these observed differences, it is recommended to optimize future study designs with respect to a parametric analysis of tinnitus duration and RI-related neural activity.

Limitations

Our study has several limitations which might be informative for future research in the specific subfield of acoustic stimulation and general research in tinnitus. No correlations between neurophysiological changes and changes in behaviorally assessed self-report tinnitus loudness

were found in our data. Given the narrow and skewed distribution of the behavioral data and the consequential arbitrary choice of a RI threshold of 50% for the responder group contrast, correlation analysis might neither way be informative with the current data. This negative result is in line with the former study of Kahlbrock and Weisz (2008).

Moreover, full and prolonged RI could only be studied in a small subset of the participants. Finally, heterogeneity of tinnitus loudness suppression curves between participants and the general low reliability and validity of tinnitus self-report data may further contribute to these absent findings.

As in many previous studies, it is challenging to recruit a large enough study sample from the locally available tinnitus population for the extensive experimental procedures. Additionally, tinnitus suppression responses, especially the parameters of RI depth as well as duration, can not be properly assessed in established screening procedures. This selection bias is hard to come by and potentially distorts results. Future studies could thus profit from internet-based prescreening. Beyond that, multi-center studies could help to further increase the validity of results aside from increasing the sample size.

Conclusion

The main goal of the current study was to unveil the oscillatory signature of RI and see how this relates to established neurophysiological models of tinnitus. In contrast to former studies, we used an extended set of modified noise stimuli targeting putatively differential neural mechanisms (i.e., RI and lateral inhibition). Furthermore, we explicitly investigated responder profiles of RI. Similar to former studies, merely a quarter of tested participants exhibited pronounced RI.

Looking at the oscillatory signature of acoustic stimulation responders and non-responders, results are indicative of decreased gamma and increased alpha power for responders. These findings are in line with both the proposed models of SLIM and TCD, respectively. These observations might be indicative of trait-specific forms of oscillatory signatures in different subsets of the tinnitus population possibly related to acoustic tinnitus suppression. In agreement with a potential transient reversal of tinnitus-specific abnormal ongoing brain activity over the course of tinnitus suppression, alpha power was enhanced in the group of responders after stimulation similarly compared to non-responders. Source localization of the sensor-level differences emphasizes the involvement of auditory cortical systems. Given the lack of correlations between tinnitus loudness and oscillatory power in this study, which was also reported by former studies, results do not allow for a conclusive interpretation with respect to

these models. The identified tinnitus patient profile experiencing RI, which mainly features less tinnitus chronification, could serve as a selection criterion to identify individuals for successful acoustic tinnitus suppression and putatively for acoustic treatments (e.g., treatment start in early stages of chronification).

Further research examining oscillatory activity during RI should strive for a healthy control group as well as control sounds not inducing RI in order to separate the neural signature of tinnitus suppression from tinnitus-unspecific neurophysiological effects.

Declaration of interest

The authors have no conflicts of interest to declare.

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5. Study 3 – Short-term tinnitus suppression with electric-field guided rTMS for individualizing rTMS treatment: a technical feasibility report

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Abstract

Background: Past research highlighted the benefits of personalized rTMS for the treatment of chronic subjective tinnitus. **Objective/ Hypothesis:** The objective was to investigate the feasibility of rTMS personalization by identifying individually optimal stimulation parameters in test sessions. Particularly, effectiveness and retest-reliability of different stimulation parameters were examined. **Methods:** Via electric-field guided rTMS, 5 patients were stimulated with different frequencies on three positions of the left and right superior temporal gyrus on two separate days. After each stimulation the patients had to evaluate tinnitus loudness and discomfort of the used protocol**. Results:** Individualization of rTMS was possible in all five patients. Significant lower tinnitus loudness was found for 1 Hz stimulation. Positive correlations between two days were observed for hemisphere (left, right), position (mSTG, pSTG) and frequency (1, 10, 20 Hz). High frequency stimulation produced high discomfort. **Conclusion:** Personalization of rTMS is considered as feasible. Consistency of parameter-specific tinnitus suppression is demonstrated.

Introduction

Current research findings in the field of neurostimulation and tinnitus are still ambiguous with respect to effectiveness of repetitive transcranial magnetic stimulation (rTMS) for the treatment of chronic subjective tinnitus (Lefaucheur et al., 2014). It remains unclear, which stimulation parameters e.g., stimulation positions or frequencies are most effective. To combat this uncertainty and also to enhance the potential efficacy of rTMS for tinnitus, two promising approaches are provided by the personalization of rTMS treatments. First, usage of neuronavigation or electric-field (e-field) guided rTMS is a putative candidate as coil positions can be defined and tracked in the range of mms over the intended target area by means of individual anatomical MRI scans (Sahlsten et al., 2017; Schoisswohl et al., 2019a). Second, during test sessions using short stimulations with reduced number of pulses, several different frequencies and positions can be tested in order to detect a patient-specific rTMS protocol for the most appropriate short-term tinnitus suppression. Compared to other neuropsychiatric disorders like depression, tinnitus offers the advantage of an immediate response to an intervention – namely changes in tinnitus loudness. The possibility to briefly suppress tinnitus by single session rTMS for a short period of time is considered as feasible (Müller et al., 2013). Identified protocols can then be used for daily treatment. The approach to focus on individual results in tinnitus research (in this case patient-specific rTMS protocols for short-term tinnitus suppression) was already emphasized by Tyler et al. (2007). So far, the concept of rTMS personalization has only been examined in a study from Kreuzer et al. (2017). Patients were stimulated throughout test sessions with 1, 5, 10 and 20 Hz, continuous theta burst stimulation along with a sham condition (200 or 50 pulses each) over the left and right dorsolateral prefrontal cortex and left and right temporo-parietal junction on both hemispheres. Responders (sham-controlled and stimulation-specific reductions) were identified and stimulated with their most effective prefrontal and temporo-parietal rTMS protocol over the course of a two-week period (4000 pulses per session). Non-responders received the standard stimulation protocol for the particular brain region. Better improvements in tinnitus-related questionnaires were found for the group which received individualized treatment as compared to the group receiving the standard protocol. This confirms the ability to identify personalized rTMS protocols and suggests the superiority of this approach for the treatment of chronic tinnitus with rTMS.

Following on from findings of this study, the hereafter reported feasibility trial investigates whether it is possible to personalize e-field guided rTMS and examines the effectiveness and retest-reliability of certain stimulation parameters in short-term tinnitus suppression. For this purpose, three different stimulation positions of the left and right superior temporal gyrus (STG)

are stimulated by an e-field guided neuronavigation rTMS system with different frequency protocols on two different days.

Material and Methods

This trial was approved by the local ethics committee of the University of Regensburg, Germany (17-820-101).

Sample characteristics

Five patients (1 female) with chronic subjective tinnitus (> 6 months tinnitus duration) and rTMS experience were enrolled in this feasibility trial. Mean age was 51.6 years (SD = 10.92), all of them were right-handers, two experienced unilateral right-sided tinnitus, whereas three suffered from bilateral tinnitus. Primary inclusion criteria were as follows: age 18 – 75; subjective chronic tinnitus; no serious medical, neurological or psychiatric disorders; stable medication; no contraindication for magnetic resonance imaging (MRI), no current tinnitus treatment or participation in other tinnitus-related experiments. All patients gave written informed consent prior to the experiment.

rTMS test session

T1 weighted MRI brain scans conducted by a MAGNETOM 1.5 tesla scanner (Siemens, Germany) preceded the experiment. Individual anatomical images in combination with an e-field guided neuronavigation rTMS system (NBT System 2; Nexstim Plc., Finland) facilitated a stimulation of patient's superior temporal gyrus (STG) with millimeter accuracy. Besides visualization and information on the strength of the induced e-field (V/m) in real time, the usage of an e-field guided rTMS system offered the opportunity to control for the direction of the induced electric current (for a detailed description of e-field guided rTMS see Sahlsten et al., 2015). Before the test sessions, patient's resting motor threshold (RMT) was defined via stimulation of the left primary motor cortex and simultaneous recordings of motor evoked potentials (MEP) from the thenar muscles of the right hand. Individual motor hotspots were detected by the administration of single pulses (maximum 30 pulses) over different positions of the left primary motor cortex, until several MEPs with a peak-to-peak amplitude of > 50 µV were detectable. The position with the highest amplitude threshold was repeated with the aid of an aiming tool implemented in the neuronavigation system (same coil orientation and tilting). Subsequently, RMT determination was performed by applying single pulses with automatically varying intensity shifts (2.5% steps up and down). RMT was specified as the minimum

stimulation intensity needed to produce MEPs with a minimum of 50 µV amplitude in at least 50% of applied pulses.

Six stimulation positions for rTMS were localized in reference to Sahlsten et al. (2017). Stimulation positions consisted of anterior (aSTG), middle (mSTG) and posterior (pSTG) parts of the left and right STG. Anterior parts were localized about one centimeter in posterior direction from the junction of sulcus centralis with the STG. PSTG was set at the temporo-parietal junction, whereas the mSTG was selected in the middle of those two points. During the test sessions, patients were stimulated with 200 pulses of 1, 10, 20 and 0.1 Hz (20 pulses, active control condition, no neuroplastic effects expected due to few pulses and long pulse intervals) rTMS with 110% RMT. Each stimulation was executed with the coil placed in such a way, that the direction of the induced e-field was perpendicular to the sulcus of the target area. The order of stimulation frequency, hemisphere and positions was randomized. After each of the 24 protocols, the patients had to rate the loudness of their tinnitus on a numeric rating scale from 0 to 110% of baseline loudness (0% represents a total absence of tinnitus, 100% no change in tinnitus loudness, whereas 110% signified an increase of tinnitus loudness by 10%) and the degree of discomfort from 0 to 10 (10 signified intolerability) induced by the rTMS interventions. To investigate reliability, the test session was repeated on a second day with a minimum interval of one day and a new randomization (in addition reversed order of hemisphere). The most suitable rTMS protocol for short-term tinnitus suppression was identified individually for each patient with respect to the induced tinnitus loudness reduction as well as discomfort rating of the respective rTMS protocol.

Statistical Analysis

Tinnitus loudness ratings for all patients were averaged for the stimulation parameters frequency, position and hemisphere and analyzed with the statistic software SPSS (SPSS vers. 24; IBM, USA). Differences in tinnitus loudness and discomfort ratings for stimulation positions and frequencies were analyzed by Friedmann tests. Significant effects were followed up by Wilcoxon tests. Wilcoxon tests were conducted to examine differences in the stimulation hemisphere. Reliability of stimulation parameters in short-term tinnitus suppression (day one and day two) was analyzed by Kendall's Tau correlations with averaging the parameters of non-interest. Statistical significance was set at $p \leq .05$. Plots were created in R (R version 3.4.3; R Foundation for Statistical Computing, Austria) with the package "ggplot2".

Results

As shown in **Table 13**, an individual best protocol for brief tinnitus suppression could be identified for each patient. Statistical analysis showed a significant effect of frequency ($\chi^2(3) = 9.98$, $p = .02$). Post-hoc tests revealed significant lower tinnitus loudness ratings of 1 Hz compared to 0.1 Hz ($z = -2.02$, $p = .04$), 10 Hz ($z = -2.02$, $p = .04$) as well as 20 Hz ($z = -2.02$, $p = .04$) with no differences between the other contrasts (all p-values > .05). No significant effects were found for stimulation position ($\chi^2(5) = 1.60$, $p = .45$) and hemisphere ($z = -.67$, $p = .50$) (compare **Figure 9a, 9d, 9g**). Statistical tests for the discomfort ratings exposed a significant effect of frequency ($\chi^2(5) = 9.98$, $p = .02$). Post-hoc Wilcoxon tests revealed significant differences between 0.1 Hz and 1 Hz ($z = -2.04$, $p = .04$), 0.1 Hz and 10 Hz, 0.1 Hz and 20 Hz, 1 Hz and 10 Hz as well as 1 Hz and 20 Hz ($z = -2.02$, $p = .04$). The sham condition followed by 1 Hz produced the least discomfort ratings. Further analysis indicated significant lower discomfort levels for left hemispheric rTMS ($z = -2.02$, $p = .04$). Near-significant differences were found for the stimulation positions ($\chi^2(5) = 5.20$, $p = .07$) (compare **Figure 9b, 9e, 9h**). Tests for loudness rating reliability discovered a positive correlation between day one and day two for the left and right hemisphere ($r_\tau = .80$, $p = .05$) and also for the stimulation positions mSTG ($r_\tau = .80$, $p = .05$) and pSTG ($r_\tau = 1.00$, $p = .05$). Likewise, significant positive correlations were found for the frequencies 1 Hz ($r_\tau = .80$, $p = .05$) 10 Hz ($r_\tau = .80$, $p = .05$) and 20 Hz ($r_\tau = .95$, $p = .05$). **Figure 9c, 9f and 9i** illustrates individual tinnitus loudness ratings for stimulation frequency, position and hemisphere over the two days.

Table 13.
Individual rTMS protocol per patient.

	Patient No.				
	1	**2**	**3**	**4**	**5**
Stimulation intensity (%)	36	24	51	30	30
Hemisphere	Right	Left	Left	Right	Right
Position	mSTG	pSTG	pSTG	aSTG	pSTG
Frequency (Hz)	1	1	10	1	1
Tinnitus loudness (% from baseline loudness)	80	90	50	80	50
Discomfort rating of rTMS protocol	3	1	3	2	0

aSTG = anterior superior temporal gyrus; mSTG = middle superior temporal gyrus; pSTG = posterior superior temporal gyrus.

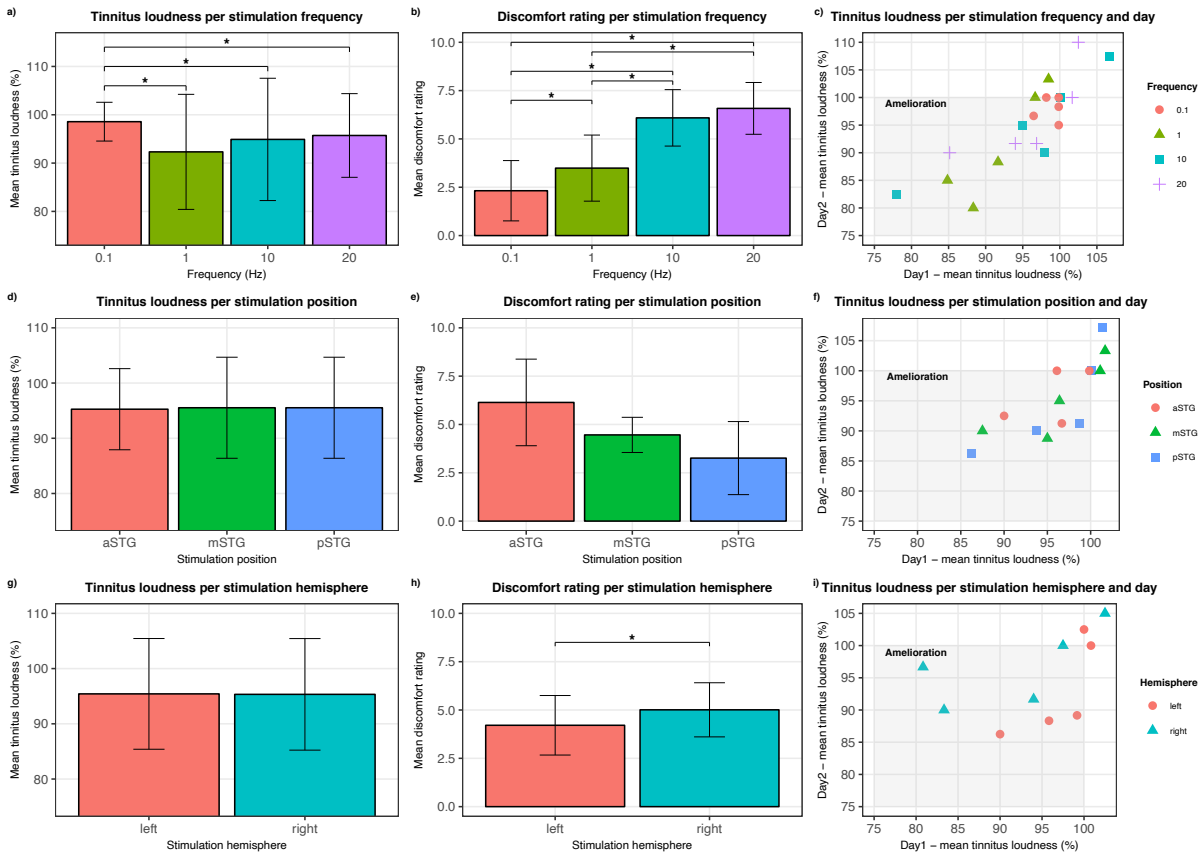

***Figure 9*. Tinnitus loudness and discomfort ratings.**
Tinnitus loudness and discomfort ratings for rTMS parameters stimulation frequency (a, b), stimulation position (d, e) and stimulation hemisphere (g, h) are illustrated. Error bars represent standard deviations. Significant differences ($p < .05$) are highlighted by *. Reliability results for the two days are outlined in c), f) and i). Tinnitus amelioration lies within the grey rectangle. Tinnitus loudness ratings for rTMS over the aSTG for day 2 are missing for one patient due to painfulness.

Conclusion

The aim of this study was to examine if a personalization of rTMS with e-field guided neuronavigation is feasible and reliable. We tested the impact of various stimulation parameters (position, frequency, hemisphere) on short-term tinnitus suppression. Since none of the patients reported superior tinnitus reduction for the sham condition, together with the possibility to identify an individual protocol for each patient, customization of rTMS protocols by performing test sessions with different protocols is considered as feasible.

With respect to retest-reliability for stimulation parameters, we demonstrated consistent tinnitus loudness ratings for hemisphere (left, right), stimulation position (mSTG, pSTG) and frequency (1, 10, 20 Hz) in tinnitus suppression. Therefore, consistency of parameter-specific tinnitus suppression can be assumed.

We also observed a significant group effect of protocol with superior effects for 1 Hz suggesting the superiority of 1 Hz over the other tested frequencies (10 Hz, 20 Hz) as a general effect, which does not depend on individual differences in susceptibility to rTMS effects.
Discomfort ratings indicate stimulations over the aSTG (one patient dropout; aSTG < mSTG < pSTG), of the right hemisphere and with high frequency protocols (0.1 Hz < 1 Hz < 10 Hz < 20 Hz) as most unpleasant. These discoveries underline the usefulness of test sessions in order to identify a rTMS protocol with best tolerability and best tinnitus suppression. On the other hand, influence of local side effects on loudness reduction cannot be excluded.
The cooling-noise of the TMS coil made it rather difficult for some patients to accurately rate loudness changes of their tinnitus during the test sessions. It is conceivable, that tinnitus loudness ratings and thereby parameter effectiveness would be different with a silent coil. Since the same coil was used for the whole trial, reliability results should not be affected. However, future test session trials should strive for bigger sample sizes, implementation of silent or uncooled TMS coils and focus either on other brain regions or one stimulation position to tackle the huge testable parameter space in rTMS.

Data availability statement

The datasets generated for this study are available on request to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by ethic commission of the University of Regensburg. The patients/participants provided their written informed consent to participate in this study. This trial was approved by the local ethics committee of the University of Regensburg, Germany (17-820-101).

Author contributions

MS, BL, and SS designed the study. MS and SS carried out the experiment and analyzed the data. SS wrote the main manuscript. All authors contributed to and reviewed the manuscript.

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6. Study 4 – Towards personalized rTMS in tinnitus: reliability of individualized stimulation protocols in behavioral and electrophysiological responses

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Abstract

Background: Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation tool potentially modulating pathological brain activity. Its clinical effectiveness is hampered by varying results and characterized by inter-individual variability in treatment responses. RTMS individualization might constitute a useful strategy to overcome this variability. A precondition for this approach would be that repeatedly applied protocols result in reliable effects. The condition tinnitus provides the advantage of immediate behavioral consequences (tinnitus loudness changes) after interventions and thus offers an excellent model to exemplify TMS personalization. **Objective**: The aim was to investigate the test-retest reliability of short rTMS stimulations in modifying tinnitus loudness and oscillatory brain activity as well as to examine the feasibility of rTMS individualization in tinnitus. **Methods:** Three short verum (1Hz, 10Hz, 20Hz; 200 pulses) and one sham (0.1Hz; 20 pulses) rTMS protocol were administered on two different days in 22 tinnitus patients. Before and after each protocol, oscillatory brain activity was recorded with electroencephalography (EEG) together with behavioral tinnitus loudness ratings. Stimulation responders were identified via consistent and sham-superior behavioral or electrophysiological responses according to the prevalent neurophysiological models for tinnitus. **Results:** It was feasible to identify individualized rTMS protocols featuring reliable tinnitus loudness changes (55% responder), alpha increases (91% responder) and gamma decreases (100% responder) respectively. Contrary, test-retest correlation analyses per protocol on a group-level were not significant neither for behavioral nor for electrophysiological effects. No associations between behavioral and EEG responses were given. **Conclusion:** RTMS individualization via behavioral and electrophysiological data in tinnitus can be considered as a feasible approach to overcome low reliability on group-level. The present results open the discussion favoring personalization utilizing neurophysiological markers rather than behavioral responses. These insights are not only useful for the rTMS treatment of tinnitus but also for neuromodulation interventions in other pathologies as our results suggest that the individualization of stimulation protocols is feasible despite absent group-level reliability.

Introduction

With a prevalence of about 10% of the population tinnitus is a rather common condition, characterized by the permanent perception of ringing or hissing in the absence of a corresponding external stimulus. The majority of tinnitus cases are caused by cochlear damages respectively hearing loss (Baguley et al., 2013; Langguth et al., 2013; McCormack et al., 2016), whereby the absence of auditory input from the periphery provokes maladaptive neural changes which ultimately manifest in hyperactivity of auditory and non-auditory cortical regions. These pathological alterations of the central nervous system are assumed to underly the perception of tinnitus (Eggermont, 2007; Eggermont and Roberts, 2012; Eggermont and Tass, 2015; Henry et al., 2014; Roberts et al., 2010).

Recent neuromodulation techniques attempt to reverse or modulate these pathological alterations (for a recent overview see Langguth, 2020). One of these is repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation tool with the capability to evoke neuroplastic changes by a rhythmic administration of brief electromagnetic pulses (Hallett, 2007; Hoogendam et al., 2010; Siebner and Rothwell, 2003). By means of low frequency rTMS it is possible to inhibit cortical excitability whereas high frequency protocols are assumed to increase cortical excitability. These statements should be seen as a rule of thumb as several findings show high inter- and intra-individual variability of rTMS with a lot of subjects not behaving accordingly (Fitzgerald, 2002; Fitzgerald et al., 2006; Klomjai et al., 2015; Rossini et al., 2015).

On this account, temporal 1Hz rTMS was applied in order to inhibit tinnitus-associated hyperactivity of the auditory cortex and consequently suppress the tinnitus percept (Eichhammer et al., 2003; Langguth et al., 2003).

For many years various treatment trials deployed left temporal low frequency rTMS showing greatly varying findings and high inter-individual variability in responses (for an overview see Schoisswohl et al., 2019). Given this backdrop, additional studies also examined the consequences of other rTMS approaches such as multi-site stimulation protocols (Lehner et al., 2016, 2013), prefrontal cortex stimulation (De Ridder et al., 2013; Noh et al., 2017; Vanneste and De Ridder, 2013) or high frequency rTMS (Forogh et al., 2014; Khedr et al., 2010, 2008) as well as continuous theta-burst stimulations (Forogh et al., 2014; Plewnia et al., 2012; Schecklmann et al., 2016) as a treatment option for tinnitus. Nevertheless, its clinical effectiveness is still not obvious. Recent reviews and meta-analyses conclude that there is no clear indication for an effect (Dong et al., 2020; Langguth, 2020; Zenner et al., 2017), while others report potential effectiveness for its clinical administration (Lefaucheur et al., 2014;

Londero et al., 2018), especially over the auditory cortex (Lefebvre-Demers et al., 2020). This lack of evidence may be explained by the fact that there is still a certain ambiguity concerning the correct rTMS parameters (e.g., frequency or position) for the application in tinnitus. Admittedly, the effects of non-invasive brain stimulation methods in general are subject to rigorous intra- and inter-individual variability, conceivably caused by a complex interplay of technical and physiological parameters (Guerra et al., 2017; López-Alonso et al., 2014; Polanía et al., 2018; Terranova et al., 2019).

A personalization of stimulation protocols might provide remedy and further enhance efficacy. Individualization of magnetic stimulation might be capable of resolving the issue of effect variability within the same type of pathology. Its implementation in neuropsychiatric research is highly dependent on phenotypes as well as the identification of appropriate and valid clinical or physiological outcome measures (Cocchi and Zalesky, 2018; Garnaat et al., 2019). However, tinnitus provides the tremendous benefit of direct reactions from the patients' side by virtue of changes in tinnitus perception and can therefore function as a kind of role model in rTMS personalization.

Test sessions (i.e., short stimulations with recording of immediate responses) and an administration of different protocols offer the opportunity to examine the ability of the different protocols to suppress tinnitus loudness in an individual. In several studies it has been demonstrated that tinnitus loudness can be suppressed by means of single rTMS sessions for some minutes (Folmer et al., 2006; Fregni et al., 2006; Lorenz et al., 2010; Meeus et al., 2009; Plewnia et al., 2003), and that suppression patterns vary among patients (Müller et al., 2013). The concept of rTMS personalization in the clinical context of tinnitus was first introduced by Kreuzer et al. (2017). By dint of rTMS test sessions with different types of frequencies and positions, individualized protocols for brief tinnitus suppression were identified and further used in the course of a daily treatment. These findings emphasize the feasibility of rTMS individualization and imply superiority over a standard treatment protocol by means of a higher number of treatment responders, even if no statistical differences between the standard and the individualized treatment were detected in this relatively small pilot study. In another preliminary work from our group using an e-field guided system we were able to demonstrate reliable tinnitus loudness decreases for certain stimulation parameters as well as the possibility to individualize rTMS characterized by a consistent and sham-controlled tinnitus loudness suppression in five out of five individuals (Schoisswohl et al., 2020a). Nonetheless, behavioral responses are governed by certain limitations such as their highly subjective matter and the

difficulty to accurately evaluate minor changes in the tinnitus percept in many cases, which might constitute an additional reason for variability in responses.

It is widely established, that tinnitus is accompanied by pathologically altered oscillatory brain activity patterns. According to the "Thalamo-cortical Dysrhythmia Model" (TCD), the assumed mechanism behind these changes are peripheral deafferentation causing thalamic low frequency activity which in turn provokes a boost in neural synchrony and increased gamma activity in auditory regions of the cortex (De Ridder et al., 2015b; Llinás et al., 2005, 1999). An expansion of the TCD model termed "Synchronization-by-Loss-of-Inhibition-Model" (SLIM), presumes that an ancillary suppression of neurons relevant for inhibition additionally causes diminished activity in the alpha frequency range. Moreover pathological gamma in tinnitus is prompted by this alpha decrease and the concomitant loss of inhibition (Weisz et al., 2007a).

Several neurophysiological investigations using electro- or magnetoencephalographic measurements revealed decreased activity in the alpha band and increased activity in the delta and gamma frequency ranges (Adjamian et al., 2012; Balkenhol et al., 2013; Moazami-Goudarzi et al., 2010; Schlee et al., 2014; Weisz et al., 2007b, 2005). In particular, gamma is suggested to be closely related to the actual tinnitus perception (De Ridder et al., 2015a; van der Loo et al., 2009; Weisz et al., 2007b). These altered spontaneous brain activities might provide a potential indicator to examine the effect of rTMS in tinnitus.

TMS-EEG investigations have already demonstrated, that rTMS successfully modulates evoked and ongoing brain activity with effects exceeding the stimulation offset (neuroplastic consequences) (Noda, 2020; Qiu et al., 2019; Thut and Pascual-Leone, 2010). In the clinical context, TMS-EEG approaches are already used for several neuropsychiatric conditions such as schizophrenia, depression or Alzheimer's disease in order to identify and investigate the relevance of neurophysiological markers as well as to provide a more profound insight into the neuroplastic consequences of rTMS (Hui et al., 2019; Tremblay et al., 2019). In case of tinnitus, a combination of rTMS and EEG might not only help to improve our understanding of the pathophysiology and altered ongoing brain activity patterns behind tinnitus but also shed light on neurophysiological markers for tinnitus suppression. As of yet, only a handful of studies investigated the consequences of single rTMS sessions on spontaneous brain activity in tinnitus. Müller et al. (2013) applied different stimulation types (1 Hz, continuous theta burst, intermittent theta burst and individual alpha frequency rTMS) over the temporal cortex and aimed to detect the most efficient protocol for transient tinnitus suppression per subject. By using magnetencephalography (MEG) they could detect a significant increase of alpha power (8 – 12 Hz) in the auditory cortex associated with tinnitus suppression. Due to the absence of

clear effects on a whole-group level, the authors emphasize the relevance of analysis on an individual subject level to unveil the key mechanisms behind tinnitus suppression. In this context, especially modulations in the alpha frequency band might provide a potential marker for future attempts in individualizing rTMS. Schecklmann et al. (2015) compared the neuroplastic consequences of rTMS in tinnitus patients with healthy controls and observed rTMS-specific modulations almost entirely for the group of tinnitus patients. A left temporal 1 Hz stimulation with 200 pulses decreased power spectra in the delta (2 – 3.5 Hz) and theta (4 – 7.5 Hz) frequency ranges as well as increased beta2 (18.5 – 21 Hz) frequency band power over frontal areas in tinnitus patients. Right prefrontal cortex 1 Hz stimulation reduced beta3 (21.5 – 30 Hz) and gamma (30.5 – 44 Hz) band activity in tinnitus patients in temporal areas. In contrast the control group exhibited enhanced beta3 and gamma power. Results emphasize the ability to modulate tinnitus-related ongoing brain activity or rather to induce neuroplastic changes in tinnitus by rTMS in accordance with the TCD model. However, on a behavioral level reliable sham-controlled decreases in tinnitus loudness were solely present in two out of 20 tinnitus patients (one after right prefrontal, one after left temporal rTMS).

Considering past findings, in particular the ability of certain rTMS protocols to transiently decrease tinnitus loudness plus modulate tinnitus-associated oscillatory brain activity, up to now there is no convincing data on test-retest reliability of the effects of single session rTMS. A test-retest design has the potential to yield essential details about effect-consistency, more specifically if rTMS produces reliable and valid modulations. Findings may promote decisions in choosing appropriate rTMS protocols for daily treatments. Due to the overall high variability of non-invasive brain stimulation effects, it is of utmost importance to identify reliable brain stimulation techniques to cope for this variability. Hence, one of the objectives of the current experiment was to scrutinize the test-retest reliability of different rTMS protocols in short-term tinnitus suppression and modifying resting state EEG activity. For this purpose the study design used in Schoisswohl et al. (2020a) with pre-post rTMS tinnitus loudness ratings was expanded by electrophysiological measures before and after each rTMS. Furthermore, it was reduced by the factor stimulation position since the majority of patients (three out of five) responded to a stimulation over temporo-parietal regions. An e-field guided stimulation over the left and right temporo-parietal junction allows for a more precise investigation of the parameter frequency, since past studies show inconsistent results in this regard.

Beyond that, we wanted to undertake further research on the personalization of rTMS by means of the model tinnitus. The aim was to assess the feasibility of identifying an rTMS protocol for consistent and sham-superior brief tinnitus suppression per patient (behavioral response). In

light of previous work from Müller et al. (2013) together with the current prevalent neurophysiological models in tinnitus, we wanted to go one step beyond and strive for a rTMS personalization based on electrophysiological responses. The specific objective was to ascertain a protocol per patient, which is able to produce consistent and sham-superior increases in alpha or decreases in the gamma frequency band (EEG response) respectively. Additionally, we were interested if an EEG response in the alpha or gamma band is related to a behavioral response and vice versa.

Material and Methods

Participants

N = 22 patients (5 female) with chronic subjective tinnitus, recruited from the Interdisciplinary Tinnitus Centre in Regensburg, Germany, participated in this experiment. Participants had to comply to the following inclusion criteria: age between 18 and 75 years; German-speaking; no or stable treatment with psychoactive drugs; absence of severe somatic, neurological or psychiatric conditions (e.g., acute psychosis, severe depression, alcohol and/ or substance abuse or known brain tumor); no simultaneous participation in other tinnitus-related experiments or treatments. Further, participants had to exhibit no contraindications with respect to TMS (e.g., epilepsy or state after traumatic brain injuries; cf. Langguth et al., 2014; Schecklmann et al., 2014) as well as magnetic resonance imaging (MRI) (e.g., heart pacemaker, vascular clamp, implanted insulin pump or severe claustrophobia). Each participant received detailed clarification about study aim, procedure and applied methods as well as potential adverse effects related to TMS and gave written informed consent before study start. The study was approved by the ethics committee of the University of Regensburg, Germany (ethical approval number: 17-820-101).

Test session procedure

Ahead of the rTMS tests sessions, participants' hearing thresholds for the frequency range of 125 Hz to 8 kHz were determined by the use of a clinical audiometer (Madsen Midimate, 622D; GN Otometrics, Denmark). In addition, structural MRI brain scans (T1) were undertaken with a MAGNETOM 1.5 Tesla scanner (Siemens, Germany) for neuronavigated rTMS and participants were requested to complete German versions of the Tinnitus Handicap Inventory (THI; Kleinjung et al., 2007; Newman et al., 1996) the Tinnitus Sample Case History Questionnaire (TSCHQ; Langguth et al., 2007) and the European School for Interdisciplinary Tinnitus Research Screening Questionnaire (ESIT-SQ; Genitsaridi et al., 2019).

The actual rTMS test sessions lasted approximately three hours and took place on two different days with a maximum inter-session interval of two days, whereby daytime was always the same (± 1 hour). Both test session days followed the same procedure. On each day, subjects were stimulated with four different rTMS protocols over the left temporo-parietal junction (TPJ) and with the same four protocols over the right TPJ (see section repetitive transcranial magnetic stimulation). Thus, a total number of 8 different rTMS protocols was applied on each test session day. Magnetic stimulation protocols were administered in a randomized sequence on each day, with the exception that the order of hemisphere was inverted (if the stimulation sequence on the first day started over the left hemisphere, it began with a stimulation over the right hemisphere on the second day). During three minutes before and after each stimulation, patients were requested to focus on their tinnitus and verbally rate the current loudness of their tinnitus perception on a numeric rating scale ranging from 0% to 110% at seven different points in time with an inter-rating interval of 30 seconds (T0, T30, T60, T90, T120, T150 and T180). The numeric rating scale was anchored at 0% (absence of tinnitus) and at 100% (usually perceived tinnitus loudness level). Concurrent to these ratings, resting state oscillatory brain activity was recorded for three minutes each by means of EEG. For this purpose, participants were instructed to sit calmly, focus on a certain point in the room and avoid unnecessarily eye blinks or muscle movements. Subsequent to each post stimulation loudness rating/ EEG recording, participants had to evaluate the level of discomfort caused by the applied rTMS protocol on a numeric rating scale from 0 to 10, whereas 10 corresponds to utmost discomfort or rather intolerability. **Figure 10** provides an illustration of the entire test session proceeding.

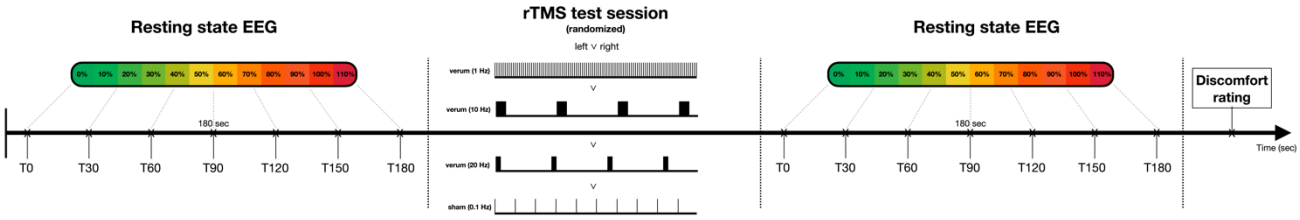

Figure 10. **Test session procedure.**
Test sessions were conducted on two different days according to the same procedure. Three different verum rTMS protocols (1 Hz, 10 Hz, 20 Hz) with 200 pulses each and one sham protocol (0.1 Hz) with 20 pulses were administered over the left and right temporo-parietal junction in a randomized order. Thus, a total number of 8 different rTMS protocols was applied on each test session day. Before and after each magnetic stimulation, participants were requested to rate the subjective loudness of their tinnitus on a numeric rating scale from 0% to 110% (0% - complete absence of tinnitus; 100% - no change; 110% - 10% loudness increase) at seven points in time (30 seconds inter-rating interval). In parallel to these ratings, resting state brain activity was recorded with electroencephalography (EEG) for three minutes. At the end of each rTMS protocol (pre-rating/ recording – stimulation – post-rating/ recording), patients had to rate the induced level of discomfort on a numeric rating scale from 0 to 10 (10 – utmost discomfort).

Repetitive transcranial magnetic stimulation (rTMS)

An e-field guided rTMS system (NBT System 2; Nexstim Plc., Finland) together with individual structural MRI scans (T1) was utilized for the test sessions. Prior to the first session, participants' resting motor threshold (RMT) was determined according to the same procedure as already described in Schoisswohl et al. (2020a). Thereby, various positions over the left primary motor cortex were stimulated until several motor evoked potentials (MEP) derived from the thenar muscles of the right hand with a peak-to-peak amplitude of > 50 µV were visible. The stimulation position with the highest MEP amplitude was repeated via the neuronavigation system and single pulses with intensity shifts were applied. The lowest stimulation intensity which produced MEPs with an amplitude of at least 50 µV in half of the administered pulses was defined as subjects' RMT. Additionally, the RMT determination was repeated with a mounted EEG cap using the same motor hotspot. Magnetic stimulation consisted of 1 Hz, 10 Hz and 20 Hz protocols with 200 pulses each at 110% RMT, whereas a series of 20 pulses at 0.1 Hz was deployed as an active control condition (sham) with no assumed neuroplastic consequences (Chen et al., 1997; Kumru et al., 2017). Each protocol was administered over the left and right TPJ, resulting in a total number of eight different rTMS protocols. An uncooled coil was used for the test sessions, as the cooled coil produces additional noise and we aimed at minimizing the stimulation noise, as it could confound both behavioral and neurophysiological effects. Stimulation positions were localized according to the electrode positions CP5 and CP6 (10-20 System). By virtue of the application of an e-field guided neuronavigation system and the opportunity for online visualization of strength and direction of the TMS-induced e-field on subjects' anatomical scans, each stimulation was administered with the induced e-field perpendicular to the sulcus of the brain area of interest. In order to ensure that the stimulation positions respectively the induced e-field remained the same over the two test sessions, both electrode positions were tagged with a digitization pen and marked on the individual anatomical images. Next, the coil was placed accordingly, a single pulse with an intensity of 10% RMT was given and the corresponding position of the coil was saved in the neuronavigation system. With the aid of a system-intern aiming tool, the exact position of the coil could be repeated with respect to centering, rotation and tilting. After each protocol the position was verified and adjusted if necessary. For safety reasons all participants were wearing in-ear plugs during the whole stimulation procedure.

Electroencephalography

Data acquisition and preprocessing

Participants' electrophysiological resting state brain activity was recorded for three minutes before and after each of the eight rTMS protocols by means of EEG with a BrainAmp DC system (Brain Products GmbH, Germany) in combination with an Easycap elastic electrode cap (Easycap GmbH, Germany) consisting of 64 electrodes placed according to the 10-20 System (GND: AFz) and the software Brain Vision Recorder 1.20 (Brain Products GmbH, Germany). EEG measurements were online referenced to FCz and recorded at a sampling rate of 500 Hz. Impedances were kept lower than 10 kΩ during the whole recording.

Preprocessing of raw EEG data was conducted with a custom-built pipeline in Matlab (Matlab R2018b; Mathworks, USA) by employing functions implemented in the EEGLAB toolbox (Delorme and Makeig, 2004). In a first step, EEG data was filtered between 1 Hz and 45 Hz and segmented into 2 second epochs. Afterwards the data was visually inspected and single epochs featuring artifacts or verbal tinnitus loudness ratings were removed from the signal. For each dataset, the first and last two epochs were rejected as well, and noisy or deviant sensors were identified for subsequent interpolation. In order to identify and reject vertical and horizontal eye movements, an independent component analysis (ICA; fastICA toolbox http://research.ics.aalto.fi/ica/fastica/) was executed. In a next step, datasets were re-referenced using an average reference and the online reference electrode FCz was reconstructed and added as a data channel. Previously identified channels with high signal-to-noise ratio were interpolated using the spherical spline method (Perrin et al., 1989). As a last step, preprocessed datasets underwent a final visual inspection.

Power spectra

Power spectra analysis was performed with the Fieldtrip toolbox (Oostenveld et al., 2011) in Matlab. Fast Fourier Transformation (FFT, "mtmfft") and a hanning window with 1 Hz spectral smoothing was used for the calculation of pre and post stimulation power spectra for each channel per rTMS protocol. Obtained power spectra underwent a normalization through a division of the spectral power of every single frequency by the average spectral power of the whole frequency spectrum. Grand averages were calculated for every pre and post stimulation dataset per channel and the following frequency bands: delta (2 – 3.5 Hz), theta (4 – 7.5 Hz), alpha (8 – 12.5 Hz), beta (13 – 32.5 Hz) and gamma (33 – 44 Hz) (Schecklmann et al., 2015; Vanneste et al., 2011). RTMS protocol specific pre-to-post power changes in the respective frequency bands were obtained by subtracting the pre stimulation from the post stimulation

power for each channel (Δ power = post – pre). Channels Iz, TP9 and TP10 which usually contain noisy signal were excluded, resulting in 60 channels for further statistical analysis.

Statistical analysis

All subsequent statistical analyses were performed with the statistics software R (R version 4.0.3; R Foundation for Statistical Analysis, Austria) using the packages "psych" and "ggstatsplot". Assumptions for parametric testing were examined with Shapiro-Wilk-Tests (normal distribution) and F-Tests (sphericity) and if violated non-parametric tests were performed. Significance levels were set to ≤ .05 for all analysis, whereby < .10 was considered as a statistical trend. Differences between left and right hearing level, RMT as well as induced e-field strength with and without mounted EEG cap were analyzed with paired sample t-tests and Wilcoxon signed-rank tests respectively.

Reliability analysis of TMS-induced tinnitus loudness changes and discomfort

Pre stimulation ratings were averaged (T0 – T180) to receive a stable tinnitus loudness baseline for each protocol per subject. TMS-induced tinnitus loudness changes were calculated via a subtraction of the mean baseline loudness level from the mean post stimulation loudness level (Δ loudness = post – baseline). Test-retest reliability of TMS-induced mean tinnitus suppression as well as discomfort evaluation over both test session days was analyzed by means of Spearman correlations for each protocol. P-values were adjusted for multiple comparisons using the Holm-Bonferroni method (Holm, 1979).

Reliability analysis of TMS-induced changes in oscillatory brain activity

Test-retest reliability of protocol-specific pre-post power spectra changes were analyzed with Spearman correlations. Therefore, the obtained changes were correlated between the first and second test session on a single sensor level per rTMS protocol and frequency band. Thus, 300 correlations were calculated per rTMS protocol (5 frequency bands x 60 sensors). Obtained p-values of sensor correlations were adjusted according to the number of sensors separated per frequency band and protocol using the Holm-Bonferroni method (Holm, 1979). In case of significant results, p-values were further corrected for the number of applied protocols akin to an adjustment for multiple comparisons of behavioral results. We were exclusively interested in positive correlation outcomes, representing reliability of TMS effects. Significant positive correlations of channel pairs were identified via correlation matrices and projected on a 60-channel topographical scalp map applying a color-coding for received correlation coefficients

(r_s). A minimum number of two neighboring electrodes featuring significant positive correlations (electrode cluster) was considered as a reliable TMS-induced change in power spectra. Triangulation of 2d sensors was utilized for neighboring sensor identification.

rTMS individualization via responder identification using behavioral and electrophysiological data

Additional to test-retest reliability analysis, rTMS individualization was examined based on single subject responses concerning loudness evaluation and electrophysiological consequences. Behavioral response to one of the verum interventions was defined as a mean tinnitus loudness suppression (compare section Reliability analysis of TMS-induced tinnitus loudness changes and discomfort evaluation) superior to sham stimulation (Δ loudness verum > Δ loudness sham) on both test session days for the same rTMS protocol and stimulated hemisphere. EEG responders were defined for the alpha (8 – 12.5 Hz) and gamma (33 – 44 Hz) frequency bands separately. In particular we were interested in alpha power increases and gamma power decreases from pre to post stimulation. As indicated in the introduction, alpha increases and gamma decreases are the most valid biomarkers for tinnitus reductions as indicated by literature review and expert knowledge. For each subject and protocol, the top 20% of channels exhibiting alpha increases/ gamma decreases were detected and scrutinized with regards to sham-superiority per day.

If a sham-superior alpha increase respectively gamma decrease was observed in the same sensor on both days plus the corresponding pattern occurred in a minimum number of two adjacent channels, the subject was designated as either alpha or gamma responder. Associations of a behavioral response to any of the eight protocols with an electrophysiological response in the alpha or gamma frequency band and vice versa were examined with Fisher's exact tests due to cell frequencies less than five.

Results

Sample characteristics

Participants were aged from 43 to 69 years (M = 57.05, SD = 6.79) and had an average tinnitus duration of 131.64 months (SD = 116.76). The majority reported a bilateral tinnitus perception as well as loudness fluctuations. No difference in hearing loss between the left and the right ear was observed, $t_{(13)} = -1.36$, $p = .198$. THI severity grades ranged from mild (grade 2) to catastrophic (grade 5) and manifested in average in severe severity (grade 4) for the whole sample (M = 58.49, SD = 19.55). As expected, the RMTs were significantly higher with a

mounted EEG cap, $p < .001$. Unexpectedly, the corresponding strength of the induced e-field was similarly higher with an EEG-cap, $t_{(21)} = -6.07$, $p < .001$. Although the motor hotspot for RMT determination was identical as well as coil centering and rotation, differences in the e-field might derive from difficulties in the adjustment of coil tilting due to distances to the scalp as well as the concomitant stimulation at higher intensities. Information about participant characteristics can be seen from **Table 14**. Besides anticipated side effects such as discomfort during rTMS (in particular by rapid muscle contraction caused by high frequency protocols) or temporary tinnitus loudness increases after stimulation, no additional side effects could be observed in the current sample. Spearman correlations showed significant positive correlations for discomfort evaluations of each applied rTMS protocol between the two test sessions (cf. **Figure S4** in the supplemental material).

Table 14.
Participants characteristics.

N (female)	22 (5)			
Handedness (left/ right/ both) (4 missings)	0/ 14/ 4			
Tinnitus laterality (left/ right/ both/ inside head) (4 missings)	1/ 1/ 14/ 2			
Tinnitus loudness fluctuation (yes/ no) (4 missings)	14/ 4			
	M ± SD	**Md**	**Min**	**Max**
Age (years)	57.05 ± 6.79	57.50	43.00	69.00
Tinnitus duration (months) (2 missings)	131.65 ± 116.79	102.00	5.00	420.00
Hearing loss left (dB) (8 missings)	23.42 ± 9.72	22.22	7.22	41.67
Hearing loss right (dB) (8 missings)	27.87 ± 14.29	23.06	7.78	61.88
THI score (0-100)	58.49 ± 19.55	58.00	30.00	90.00
Tinnitus loudness (%) (6 missings)	70.31 ± 19.87	80.00	30.00	90.00
RMT (%)	33.95 ± 5.33	33.00	25.00	46.00
RMT (%) + EEG cap	41.91 ± 9.65	41.00	30.00	66.00
Electrical field (V/m)	54.47 ± 13.90	52.50	27.00	86.00
Electrical field (V/m) + EEG cap	66.66 ± 15.38	66.25	44.00	99.00

M = mean; SD = standard deviation; Md = Median; Min = minimum; Max = maximum; THI = Tinnitus Handicap Inventory; RMT = resting motor threshold, EEG = Electroencephalography.

Test-retest reliability of TMS-induced changes in tinnitus loudness and oscillatory brain activity

No significant correlations were observed for the two test session days with regards to mean tinnitus loudness changes for any of the protocols (cf. **Figure 11**). It should be noted, that without considering corrections for multiple comparisons, a significant test-retest reliability was found for left hemispheric stimulation with 10 Hz and right hemispheric stimulation with 20 Hz.

On the basis of our predefined reliability criteria, reliable changes in oscillatory brain activity were solely present for 1 Hz stimulation of the right TPJ, exclusively for the gamma frequency band. As can be seen from **Figure 12**, these reliable changes were primarily observed over parieto-occipital regions, whereby neighboring channels PO7 and O1 constitute a significant reliable cluster. If corrected for multiple comparisons, this effect disappears and is therefore only conditionally interpretable.

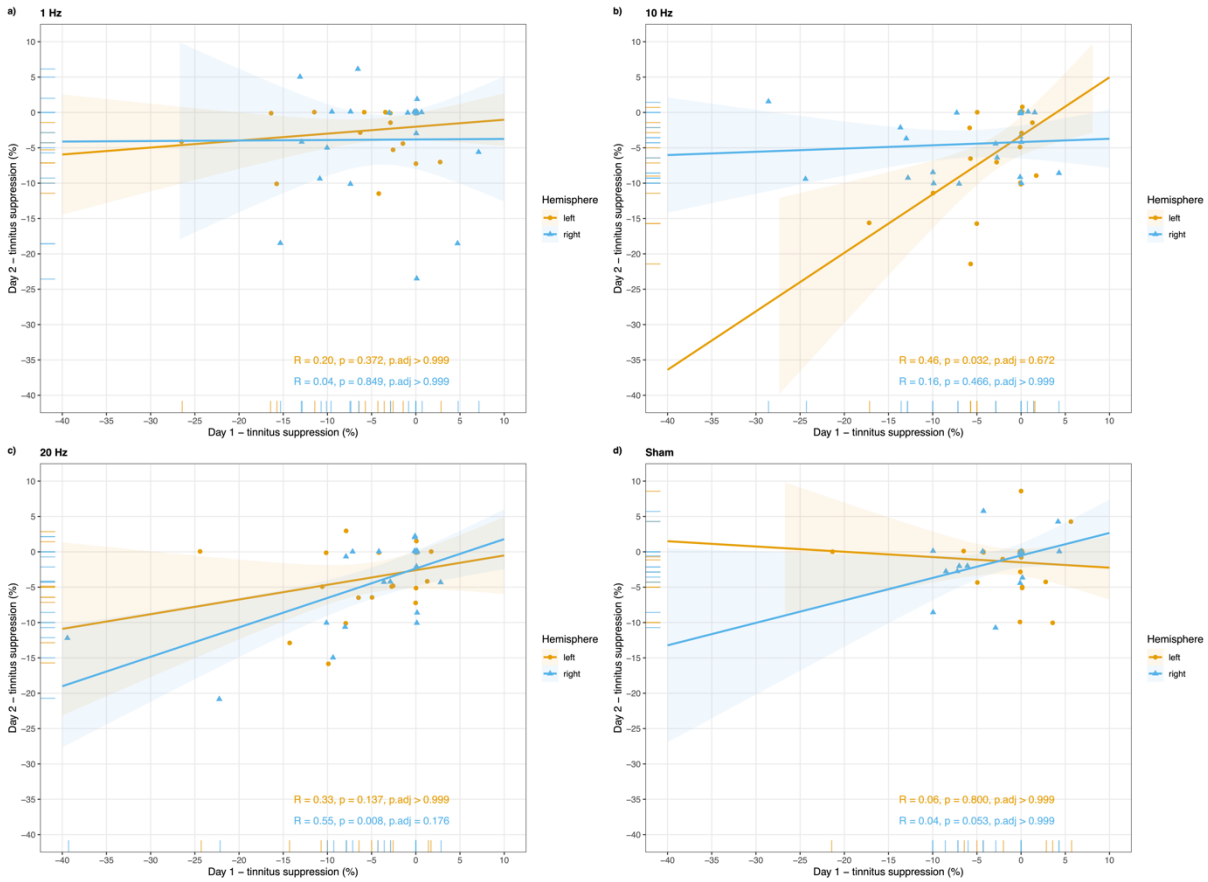

***Figure 11*. Group-level reliability of TMS-induced changes in tinnitus loudness.**
Spearman correlations of rated tinnitus suppression (%) per rTMS protocol between the first and the second test session day are illustrated. Colored ribbons represent confidence intervals (95%). Reliable changes were observed for a (b) 10 Hz stimulation over the left temporo-parietal junction and a (c) 20 Hz stimulation over the right temporo-parietal junction. Both correlations do not withstand a correction for multiple comparison and should therefore not be overrated and interpreted only exploratively.

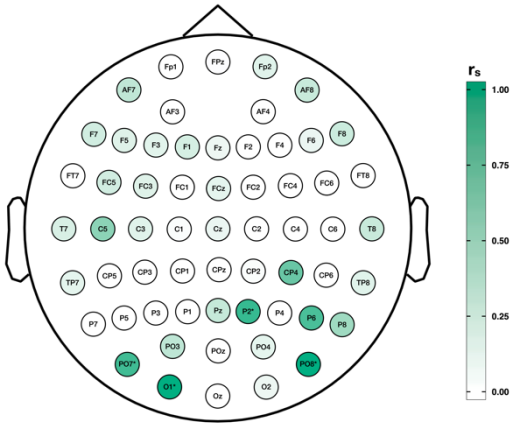

***Figure 12*. Group-level reliability of TMS-induced changes in oscillatory brain activity**
Spearman correlations coefficients (r_S) of right hemispheric 1 Hz rTMS-induced changes in the gamma frequency band (33 – 44 Hz) for the two test session days are projected on a topographical map per electrode. Significant reliable electrodes are highlighted with asterisks. Separate reliable changes are primary present over parieto-occipital electrodes, whereby neighboring channels PO7 and O1 form a significant reliable cluster. However, this effect disappears after a correction for multiple comparison and is therefore only conditionally interpretable.

rTMS individualization using behavioral and electrophysiological data

In 12 out of 22 participants it was possible to identify an individualized rTMS protocol for short-term tinnitus suppression characterized by sham-superiority on both test session days. From those 12 patients 10 (83.33%) responded to more than one stimulation type. Detailed information about individual responses together with the induced mean tinnitus suppression (averaged over both test session days) can be found in **Table 15**. As presented in **Table 16**, the majority of subjects responded to a stimulation over the left TPJ with 20 Hz (n = 7) and 10 Hz (n = 6), and over the right TPJ with 20 Hz (n = 5). EEG responders were defined by sham-superior alpha power increase or gamma power decrease in minimal two neighboring electrodes on both test sessions. Using this criterion 20 alpha responder were identified, showing alpha power increases for at least one of the six used verum protocols. Left TPJ stimulation with 10 Hz (n = 10) or 1 Hz (n = 9) and right TPJ stimulation with 10 Hz (n = 7) produced the most alpha responders (cf. **Table 16**). Electrophysiological responses in the gamma band were present in each investigated subject for at least one protocol. Subjects responded mainly to left TPJ stimulation with 10 Hz (n = 13) or 1 Hz (n = 10) and right TPJ stimulation with 10 Hz (n = 8) or 1 Hz (n = 8) (cf. **Table 16**). Interestingly, 75% of alpha and gamma responders showed consistent power increases/decreases for more than one protocol. **Table 15** presents an overview of alpha increases and gamma decreases per rTMS protocol on a single subject level. Fisher's exact tests showed no significant association neither for behavioral responders with alpha or gamma responders nor the other way around.

Table 15.

Individual test session responses per protocol – behavioral and EEG responder.

Subject	Behavioral responder				Alpha (8 - 12.5 Hz) / Gamma (30.5 - 44 Hz)			
		1Hz	10Hz	20Hz		1Hz	10Hz	20Hz
1	Left	12.86	-	-	Left	-	↓γ	↑α↓γ
	Right	17.15	-	-	Right	-	↓γ	-
						1Hz	10Hz	20Hz
2		-			Left	↑α↓γ	↑α↓γ	-
					Right	-	-	-
		1Hz	10Hz	20Hz		1Hz	10Hz	20Hz
3	Left	3.98	-	3.71	Left	↑α↓γ	↑α	-
	Right	-	-	-	Right	↓γ	-	-
		1Hz	10Hz	20Hz		1Hz	10Hz	20Hz
4	Left	-	10.35	-	Left	↑α↓γ	-	-
	Right	-	9.28	25.71	Right	-	-	-
		1Hz	10Hz	20Hz		1Hz	10Hz	20Hz
5	Left	-	16.42	-	Left	↑α	↓γ	↑α
	Right	10.00	16.79	21.42	Right	-	-	-
		1Hz	10Hz	20Hz		1Hz	10Hz	20Hz
6	Left	-	10.71	-	Left	↑α	-	↑α
	Right	-	-	-	Right	-	↑α↓γ	-
						1Hz	10Hz	20Hz
7		-			Left	-	↑α	-
					Right	-	↑α	↑α↓γ
		1Hz	10Hz	20Hz		1Hz	10Hz	20Hz
8	Left	-	6.07	8.93	Left	-	↑α↓γ	↓γ
	Right	-	4.64	9.28	Right	-	↑α	-
		1Hz	10Hz	20Hz		1Hz	10Hz	20Hz
9	Left	-	-	3.93	Left	↑α↓γ	↑α↓γ	↑α↓γ
	Right	7.55	-	-	Right	↓γ	-	-
		1Hz	10Hz	20Hz		1Hz	10Hz	20Hz
10	Left	15.36	-	5.71	Left	↓γ	↑α	↓γ
	Right	-	-	-	Right	-	↓γ	↑α↓γ
						1Hz	10Hz	20Hz
11		-			Left	↑α	-	-
					Right	↓γ	↑α↓γ	↑α
						1Hz	10Hz	20Hz
12		-			Left	-	-	-
					Right	-	↑α	↓γ
						1Hz	10Hz	20Hz
13		-			Left	↓γ	↑α↓γ	-
					Right	↑α↓γ	↓γ	-
						1Hz	10Hz	20Hz
14		-			Left	↑α	↓γ	↑α↓γ
					Right	↓γ	-	↑α
						1Hz	10Hz	20Hz
15		-			Left	↓γ	↑α	-
					Right	↓γ	-	-
		1Hz	10Hz	20Hz		1Hz	10Hz	20Hz
16	Left	-	5.00	12.85	Left	-	↑α↓γ	-
	Right	-	-	10.00	Right	-	↑α	↓γ
						1Hz	10Hz	20Hz
17		-			Left	-	↓γ	-
					Right	↑α	↓γ	↑α↓γ
						1Hz	10Hz	20Hz
18		-			Left	↓γ	↓γ	↑α↓γ
					Right	↑α↓γ	↑α	-
		1Hz	10Hz	20Hz		1Hz	10Hz	20Hz
19	Left	-	13.57	13.57	Left	↑α	↓γ	-
	Right	-	-	-	Right	↑α	↓γ	↑α
						1Hz	10Hz	20Hz
20		-			Left	↓γ	↓γ	-
					Right	-	-	-
		1Hz	10Hz	20Hz		1Hz	10Hz	20Hz
21	Left	-	-	-	Left	-	-	↓γ
	Right	7.14	-	3.93	Right	↓γ	↓γ	↓γ
		1Hz	10Hz	20Hz		1Hz	10Hz	20Hz
22	Left	-	-	7.85	Left	↓γ	↑α↓γ	-
	Right	-	-	-	Right	-	-	-

Table 16.

Summary of behavioral and electrophysiological responder per rTMS protocol.

	T0 - T180	**↑Alpha**	**↓Gamma**
Total number of responders	12	20	22
Number of responders per protocol (N)			
Left 1 Hz	3	9	10
Right 1 Hz	4	4	8
Left 10 Hz	6	10	13
Right 10 Hz	3	7	8
Left 20 Hz	7	6	7
Right 20 Hz	5	6	6

Electrodes featuring sham-superior alpha/gamma modifications on both days are presented in **Figure 13** and **Figure 14** by means of topographical maps displaying the quantity of electrodes within alpha and gamma responders per rTMS protocol. It is apparent from **Figure 13** that alpha responses primary appeared in parieto-occipital regions on both hemispheres, whereas responses in the gamma range were especially present over frontal regions bilaterally and to some extent over parieto-occipital parts as outlined in **Figure 14**. Detailed electrode information per subject and rTMS protocol, can be found in the supplementary material for alpha (**Table S14**) and gamma responder (**Table S15**).

Discussion

The goals of this experiment were to ascertain, whether it is possible to identify treatment protocols, that provide reliable effects both on the behavioral and on the electrophysiological level, as this is a precondition for individualizing treatment. We performed two test sessions at which six active and two sham protocols were administered. We evaluated reliability by comparing tinnitus suppression effects and electrophysiological effects on an individual level by responder identification. Moreover, we performed whole-group analysis in which we correlated the behavioral and electrophysiological effects of all stimulation protocols between both test sessions.

The main finding of our study was, that in 12 out of 22 patients we could identify a stimulation protocol that reduced tinnitus loudness transiently in both sessions reliably more than sham stimulation. When we defined response by the effects on oscillatory brain activity, the number got even higher with 20 out of 22 patients in which a specific rTMS protocol increased alpha more than sham and with 22 out of 22 in which a specific rTMS protocol decreased gamma more than sham.

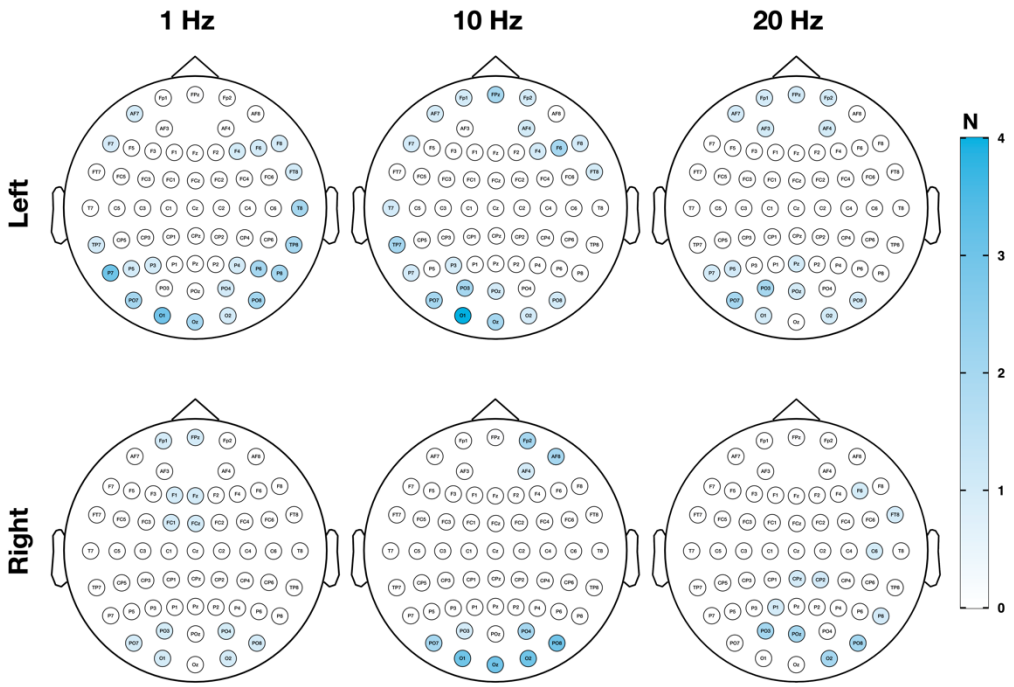

***Figure 13*. Topography of single-subject electrophysiological reliability – alpha responder**
Topography and quantity of significant reliable sensors per rTMS protocol within alpha responder. Responses in the alpha frequency band (8 – 12.5 Hz) to one of the verum protocols primarily occurred over parieto-occipital electrodes.

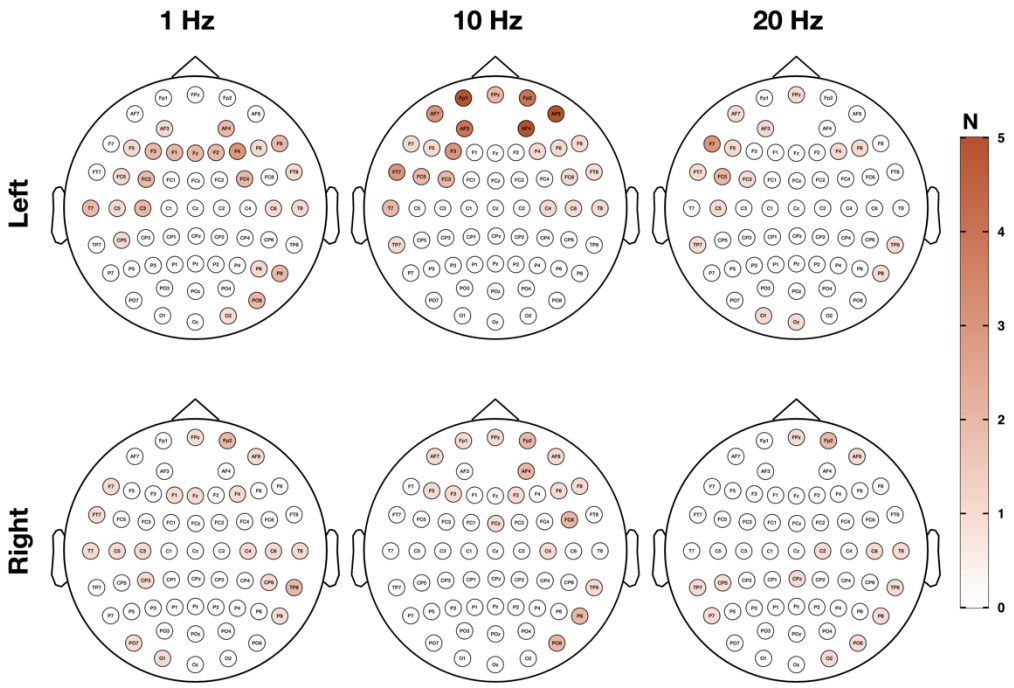

***Figure 14.* Topography of single-subject electrophysiological reliability – gamma responder**
Topography and quantity of significant reliable electrodes per rTMS protocol within gamma responder. Responses in the gamma frequency band (33 – 44 Hz) to one of the verum protocols mostly appeared over frontal electrodes on both hemispheres and partially over parieto-occipital sensors.

Correlation analysis for the whole group revealed reliable changes in tinnitus loudness after left TPJ stimulation with 10 Hz and right TPJ stimulation with 20 Hz. With respect to modulatory effects of rTMS on oscillatory brain activity, reliable changes could be obtained after right TPJ stimulation with 1 Hz in the gamma frequency band over parieto-occipital regions. However, these findings do not withstand a correction for multiple comparison and should therefore not be overrated and interpreted only exploratively.

Nevertheless, the observed effect of rTMS on gamma activity fits well with a previous TMS-EEG study where right frontal 1 Hz rTMS decreased gamma band activity over right temporal regions in tinnitus patients, whereas it increased gamma activity in healthy controls (Schecklmann et al., 2015). Gamma activity is supposed to be strongly connected with tinnitus perception (De Ridder et al., 2015a; van der Loo et al., 2009; Weisz et al., 2007b). However, as mentioned above, the effects of the first and the second session were not significantly correlated when statistical corrections for multiple comparisons were performed.

Taking our findings together we can conclude that it is possible to identify responders for specific rTMS protocols, who demonstrate a reliable behavioral or electrophysiologic response on a specific rTMS protocol. However, if we investigate the effects of a given protocol for the whole sample, the variability of the effect is relatively large from session to session.

Presumably the effects depend on the brain state before or during rTMS (Siebner et al. 2004) and this brain state might vary from session to session. In the current study the study design with six active and two sham protocols per session might have increased this variability, as after-effects from preceding protocols cannot be excluded as confounding factors.

The limited test-retest reliability corroborates the claim, that effects of rTMS in general (Maeda et al., 2000; Nettekoven et al., 2015; Polanía et al., 2018; Sommer et al., 2002; Terranova et al., 2019) but also treatment effects in tinnitus (Langguth, 2020; Soleimani et al., 2016) are subject to high variability. Thus, it is most likely that single subject impacts simply do not transfer to statistical analysis on a group level, highlighting the need and importance of personalized rTMS approaches.

On the other hand, it has been demonstrated that patients, who benefit once from rTMS have a high chance to benefit from repeated rTMS treatment (Lehner et al., 2015; Rachid, 2018).

This clinical observation fits with our finding to identify treatment responders to specific rTMS protocols.

Our results corroborate also findings from several previous studies in which the feasibility of a customization of rTMS for tinnitus via test sessions has been demonstrated (Kreuzer et al., 2017; Schoisswohl et al., 2020a). The responder rate of 55% in our study (12 out of 22) is in a

similar range as in two previous studies (Kreuzer et al. (2017) - 50% responder; Schoisswohl et al. (2020a) - 100% responder). However, both studies deployed magnetic stimulations over either prefrontal cortical regions or different positions over the superior temporal gyrus, whereas the current study targeted only a single region of the temporal cortex. The present goal was to examine the parameter frequency in more detail. Interestingly the vast majority of participants responded to high frequency stimulations over the left TPJ. It is assumed that high frequency protocols produce increases of cortical excitability (Klomjai et al., 2015). Consequently, high frequency rTMS is most likely not able to reduce tinnitus-associated temporal hyperactivity. But it has been suggested, that the induced effects can vary or shift across different targets of the cortex (Lorenz et al., 2010) and are dependent on the intrinsic state of the brain region prior to stimulation (Siebner et al., 2004; Silvanto and Pascual-Leone, 2008; Weisz et al., 2014, 2012). Based on this it could be the case that pathological auditory cortex hyperactivity as an intrinsic state of the "tinnitus brain" might cause a reversal of supposed high frequency effects (shift from excitatory to inhibitory). In accordance with the present results, previous studies have demonstrated responder rates between 40% and 57% in single session experiments with high frequency stimulation protocols (De Ridder et al., 2005; Folmer et al., 2006; Fregni et al., 2006; Plewnia et al., 2003). Likewise treatment studies with high frequency rTMS over the temporo-parietal cortex were able to show significant reductions in tinnitus distress (Khedr et al., 2010, 2008).

In addition to an rTMS individualization based on behavioral responses, the current investigation has striven for a novel attempt in rTMS individualization with objective measures. By the use of TMS-EEG combinatory measurements, we wanted to overcome the limitations of subjective tinnitus loudness ratings and identify personalized rTMS protocols via sham-superior increases in alpha respectively decreases in gamma frequency band power in at least two neighboring EEG electrodes on both test session. The utilization of especially these frequency bands as an electrophysiological response indicator is based on current neurophysiological models. In tinnitus pathological diminished alpha band activity was observed in contrast to healthy controls (Weisz et al., 2007b, 2005), whereby during states of brief tinnitus suppression either after sound stimulation (King et al., 2020) or after rTMS (Müller et al., 2013) increases in alpha power were detected. While gamma band activity is assumed to underly the actual tinnitus perception (De Ridder et al., 2015a; Weisz et al., 2007b) by associations with tinnitus loudness (Balkenhol et al., 2013; van der Loo et al., 2009). Interestingly, we were able to identify a substantially higher number of EEG responders than behavioral responders. For a total number of 20 participants, it was possible to detect an alpha

response for at least one rTMS protocol, whereas the entire sample featured responses in the gamma frequency band. Noteworthy, the quantity of alpha or gamma responders was almost twice as much as for behavioral responders. In line with our behavioral observations, a left 10 Hz stimulation resulted in the highest quantity of alpha and gamma responders. It has been shown that this type of stimulation can modulate alpha oscillations (Thut et al., 2011) and that alpha and gamma oscillations show a strong interplay not only in tinnitus (Wagner et al., 2019; Weisz et al., 2007a).

Since neurophysiological investigations were able to demonstrate relationships of the alpha and gamma band with tinnitus loudness (Balkenhol et al., 2013; King et al., 2020; van der Loo et al., 2009; Müller et al., 2013), we addressed the question if a response in the alpha or gamma band is associated with a behavioral response and vice versa. Our analysis did not reveal any relationship of EEG and behavioral responders, hampering the interpretability of our alpha and gamma findings as relevant for tinnitus loudness decreases in the current sample. A potential explanation for this lack of association could derive from the possibility, that rTMS-specific modulations/ neuroplastic consequences as measured with EEG simply do not instantly translate into behavioral responses. Consequently, longer periods of stimulation with an individualized rTMS protocol based on patients' EEG response (protocol with strongest alpha increase/ gamma decrease) for example within the course of a daily treatment, might accumulate over time into behavioral effects and could tackle the deficiency of effectiveness in current rTMS treatment trials for tinnitus.

Future studies should strive for a systematic implementation of test session approaches and investigate the therapeutic consequences of personalized rTMS in more detail. The present experiment underscores the feasibility of rTMS individualization via behavioral or electrophysiological responses. The results and methodology described in this sample of tinnitus patients might encourage neuromodulation attempts in other pathologies to personalize rTMS in order to account for inter-subject variability in rTMS response.

Conclusion

The aim of this investigation was to examine the feasibility of rTMS individualization in tinnitus. This involved the identification of responders to specific rTMS protocols and the assessment of test-retest reliability of rTMS effects in tinnitus suppression and ongoing brain activity. We were able to demonstrate the feasibility of rTMS individualization by using test sessions with different rTMS protocols. Responses to specific protocols based on electrophysiological signatures could be identified in all patients, responses based on behavioral

effects in the majority of patients. In contrast test-retest reliability as assessed with correlation analyses for the various rTMS protocols were rather low both for behavioral and electrophysiological effects.

Taken together these findings are highly encouraging for efforts to enhance the efficacy of rTMS by personalizing stimulation protocols.

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Conflicts of interest

The authors declare that they have no conflict of interest associated with this publication and there has been no significant financial support that could have influenced the outcomes. Author TH received a one-time travel cost coverage by Nexstim Plc. for an oral presentation.

7. Concluding discussion

7.1. Summary of studies and retrospective discussion

The aim of the present thesis was to investigate the impact of various short acoustic stimulation techniques and short rTMS protocols on brief tinnitus loudness suppression in order to gain more insights behind the underlying mechanisms of tinnitus loudness reductions as well as tinnitus perception per se. All four experiments conducted in the present thesis furthermore address the subject of intervention personalization in tinnitus, whether by the adjustment of noise stimulation for RI induction according to the individual tinnitus characteristics or the identification of a patient-specific rTMS protocol for transient tinnitus suppression in test sessions. In the subsequent two sections, the objectives and main findings from each experiment are summarized and discussed in an additional joint discussion per overarching topic.

7.1.1. Acoustic stimulation – study 1 and 2

The aim of the first study (Schoisswohl et al., 2019b) was to assess the effects of different amplitude-modulations and filters applied to white noise on RI in tonal and noise-like tinnitus patients. Noise stimuli were personalized according to patients' tinnitus frequency or noise bandwith using either pure tone or noise-band matching. It was demonstrated that each used stimulus provides the possibility to induce RI. No differences among stimuli in transient tinnitus loudness suppression were detected. However, superior loudness suppression for patients with noise-like tinnitus was observed directly towards stimulation. As already outlined in the discussion of study 1, this group difference might derive from observed differences in tinnitus loudness, filter adjustments or even the involvement of the non-tonotopic extralemniscal system in noise-like tinnitus (De Ridder et al., 2007; Møller, 2006). Similarly study 2 (Schoisswohl et al., 2020b) investigated the effects of different individualized filtered noise stimulations in RI. Moreover, the objective was to clarify if changes in spontaneous brain activity are a function of tinnitus loudness ratings and if different stimuli trigger different oscillatory brain activity patterns. Further, an additional comparison of EEG activity between acoustic stimulation responder and non-responder ought to provide profound insights in ongoing brain activity related to RI. Each stimulus resulted in brief tinnitus loudness suppression, whereby IBP followed by standard WN produced the strongest RI potentially caused by a decline of neural response gain and tinnitus-associated hyperactivity (Schaette et al., 2010) or feed-forward inhibition (Roberts et al., 2010).

With respect to EEG activity, neither stimulus-specific differences in ongoing brain activity nor correlations of behavioral and neural data were present, suggesting tinnitus-unspecific

neurophysiological reactions to sound stimulation as indicated by previous work (Crone et al., 2001; Joliot et al., 1994; Weisz et al., 2011).

Contrasts between acoustic stimulation responders and non-responders manifested in enhanced alpha and diminished gamma band activity in the group of responders in line with the current neural models for tinnitus. In light of observed differences in sample characteristics, namely shorter tinnitus duration for the subgroup of responders, these electrophysiological differences are suggested to represent a potential neural trait of tinnitus chronification. There is also the possibility that the differences between responders and non-responders are simply related to a neural trait of acoustic stimulation response respectively ability to induce RI in a subset of patients. Post stimulation contrasts revealed higher theta, alpha and beta activity with the strongest activity in the alpha range localized in auditory cortical areas partially in accordance with the assumption of transient reversion of pathological oscillatory brain activity during RI (Kahlbrock and Weisz, 2008) or the neural models for tinnitus (Weisz et al., 2007a).

On a whole group level, behavioral findings of both experiments appear in a similar manner. Averages of tinnitus suppression ratings per stimulus exhibit only moderate to little suppression depth. The strongest tinnitus loudness suppression took place directly after stimulation offset and normalized gradually with progression of time. Same observations were already made by previous investigations in the field (Neff et al., 2019b, 2017; Roberts et al., 2008).

Considering single subject responses, a strong heterogeneity with respect to induced tinnitus loudness changes emerged, which ranged from strong suppressions even up to tinnitus loudness increases after stimulation. It is well-known, that RI cannot be induced in every tinnitus patient (Fournier et al., 2018; Roberts et al., 2008; Vernon and Meikle, 2003) and that even brief tinnitus loudness increases can occur referred to as residual excitation (Sedley et al., 2012).

Given these disparities, only minor to moderate average suppression patterns can be observed hampering the analysis of stimulus-specific consequences on a behavioral as well as on a neurophysiological level in the current studies. Further, the variety of stimulation responses could also translate into a lack of behavioral and electrophysiological correlations in the present and past experiments (e.g., Kahlbrock & Weisz, 2008). Pre-screenings with respect to RI induction prior the actual experiments could have the potential to overcome these drawbacks by identifying an appropriate sample. RI is considered a reliable sensation (Deklerck et al., 2019). The detection of patients' MRIL recently suggested by Fournier et al. (2018) provides a fast and promising method for an evaluation of the possibility to induce RI in certain tinnitus patients.

In study 2 acoustic stimulation responder were identified according to their level of RI. Based on a previous paper, a similar but less stringent cut-off for RI induction was used. Kahlbrock & Weisz (2008) defined RI as 50% tinnitus loudness suppression for a minimum of 30 seconds after stimulation, whereas in the present study 2 RI was defined as 50% tinnitus loudness suppression directly after stimulation (Schoisswohl et al., 2020b). The quantity of responders appears to be identical for both studies. However, it is very likely that the usage of a more strict threshold for RI would consequently result in a rather small group of tinnitus patients with acoustic stimulation response respectively experiencing RI. Currently, there is no reasonable and profound consensus of a definition for RI. Although RI is listed in recent guidelines for the diagnosis, assessment and treatment of tinnitus under further assessments (Cima et al., 2019), there is a lack of categorization or threshold for RI. Accordingly, temporary suppression patterns varying from very low (e.g., 5% tinnitus loudness reduction) to a total absence of tinnitus perception could potentially defined equally as RI, highlighting the need for a clear definition.

In study 2 it was apparent from sample characteristic differences between acoustic stimulation responders and non-responders, that the group of responders showed less tinnitus chronification and lower tinnitus loudness (Schoisswohl et al., 2020b). A similar pattern in sample characteristic differences has been observed in study 1 (Schoisswohl et al., 2019b).

Patients with noise-like tinnitus showing stronger tinnitus loudness suppression towards acoustic stimulation than tonal tinnitus patients also exhibited significant shorter tinnitus durations or lower levels of tinnitus loudness akin to responder non-responder contrasts in experiment 2. This coincidence emphasizes the role of sample characteristics as a potential factor related to acoustic stimulation response and raises the question of whether RI can be predicted using patient characteristics such as tinnitus duration or tinnitus loudness.

Using a retrospective analysis of tinnitus patients participating in a randomized clinical trial which evaluated the effectiveness of tinnitus masking and Tinnitus Retraining Therapy, differences in treatment responders and non-responders were revealed. Interestingly, responders were younger and showed lower tinnitus duration (Theodoroff et al., 2014) similar to the present findings in short-term acoustic tinnitus suppression. Likewise, age (theoretically accompanied by longer tinnitus durations) or noise reactiveness (highlighting the need for pre-screenings) was identified as a significant predictor for response to sound-related treatments (Simoes et al., 2019). Further insights come from rTMS research, which demonstrates tinnitus duration as an important factor for treatment response (Khedr et al., 2008; Kleinjung et al., 2007b) as well as short-term tinnitus suppression (De Ridder et al., 2005). Up to now, attempts

to predict the ability to induce RI via patient characteristics are almost non-existent. Besides the absence of personality as a predictor for RI, a pooled analysis with data gathered from two acoustic stimulation experiments (one reported in the present thesis) failed to identify tinnitus duration as a significant predictor (Hafner et al., 2020). This finding diminishes the relevance of tinnitus duration as an important factor for acoustic stimulation response, which is in line with the results from a predictor analysis in TMS research and the lack of tinnitus duration plus any demographic or clinical characteristic as a significant response factor (Lehner et al., 2012). Nevertheless, the present findings in RI might be exemplary for treatment onsets in early stages of chronic tinnitus reporting higher intervention responses as outlined above.

It could also be conceivable that tinnitus duration is indirectly related to acoustic stimulation responses as demonstrated in study 2 by means of differences in tinnitus duration alongside with differences in spontaneous brain activity in the alpha and gamma frequency bands between acoustic stimulation responders and non-responders. Past neuroimaging studies already demonstrated pathological brain activity changes with progressing tinnitus chronification (Lan et al., 2021; Schecklmann et al., 2013a; Schlee et al., 2009a; Vanneste et al., 2015).

Tinnitus patients with advanced chronification grades might feature more robust pathological alterations e.g., lower alpha and higher gamma power in spontaneous brain activity making it infeasible to temporary reverse this activity by acoustic stimulation techniques and consequently do not induce RI as demonstrated in the current experiments. For example Schlee et al. (2014) observed lower variability of alpha activity in auditory regions in tinnitus patients with advanced tinnitus chronification. Further, a negative relationship of tinnitus duration and the ability to induce RI was demonstrated in normal hearing tinnitus patients (Hu et al., 2020). However, recent work from Riha et al. (2020) found no impact of tinnitus duration on resting state EEG activity highlighting the need of further research on the changes in oscillatory brain activity with advancing tinnitus duration.

In light of the differences in oscillatory brain activity between acoustic stimulation responders and non-responders plus the stated assumption of a trait-like oscillatory signature related to RI induction in a subset of tinnitus patients, future studies should strive for an in-depth investigation of neurophysiological predictors of RI. In a novel attempt it was feasible to predict the ability of RI induction using EEG measurements in a rather small sample of patients (Sanders et al., 2021). Moreover, future RI experiments should encompass comparisons of tinnitus patients with healthy controls in acoustic stimulation paradigms as already suggested in a study protocol by Hu et al. (2019) in order to separate the neurophysiological consequences related to RI from ordinary neural reactions to sound stimulation.

7.1.2. rTMS – study 3 and 4

Both rTMS experiments focused on the personalization of rTMS via single sessions. Experiment 3 (Schoisswohl et al., 2020a) was a technical feasibility study and investigated the feasibility and reliability of rTMS individualization in a small tinnitus patient sample. Three different targets of the superior temporal gyrus over the left and right hemisphere were stimulated with several frequencies on two days. It was feasible to individualize rTMS for each patient via brief changes in tinnitus perception. Further, consistent changes in tinnitus loudness could be demonstrated for certain rTMS parameters in particular stimulation frequency - each verum stimulation frequency resulted in reliable tinnitus loudness changes.

Succeeding study 4 (Schoisswohl et al., 2021) systematically examined the insights gained from study 3 using a bigger sample of tinnitus patients, focused on only one temporal cortex stimulation position and applied concurrent measures of electrophysiological brain activity. In view of high variability of rTMS effects, the specific aim was to investigate the test-retest reliability of certain rTMS parameters in short-term tinnitus suppression and modulating oscillatory brain activity as well as the feasibility of rTMS individualization via single subject responses. Besides rTMS personalization based on behavioral responses, electrophysiological data was used to personalize rTMS according to neurophysiological models for tinnitus.

Reliable changes in tinnitus loudness after high frequency stimulations over the left or right TPJ as well as reliable changes in the gamma frequency band after a right-hemispheric low frequency stimulation were observed, which all do not withstand a correction for multiple comparisons and should therefore only be interpreted with caution.

Individualization of rTMS was feasible in more than half of participants using tinnitus loudness ratings, whereas personalization via electrophysiological responses was found to be a superior approach. Almost the entire sample featured responses in the alpha and gamma frequency band. However, no associations of behavioral and electrophysiological responses were apparent.

There are substantial differences in the quantity of responder between the two experiments. It is very probable that the examination of a bigger sample in study 4 simply entails more inter-subject variability in rTMS response as reported in past studies (Langguth, 2020) and therefore resulted in a lower percentage of single session responders. Another potential reason could be the investigation of a reduced number of stimulation targets in study 4 compared to study 3. Anyhow, the present findings emphasize the ability to identify personalized rTMS for brief tinnitus suppression and are in accordance with previous investigations (Kreuzer et al., 2017).

Both experiments are the first of their kind in evaluating the test-retest reliability of rTMS-induced effects in short-term tinnitus suppression as well as oscillatory brain activity. Study 3 demonstrated consistent effects of certain stimulation parameters on a behavioral level, whereas in study 4 reliable changes were not observed. The absence of solid reliable findings in study 4 supports the assumption that rTMS effects are subject to high inter-individual variability (Polanía et al., 2018; Soleimani et al., 2016). As already explained in the discussion section of study 4, demonstrated single case responses might not carry over to statistical analyses on a whole group level due to inter- and intra-subject effect variability. This observation emphasizes the relevance and necessity of rTMS individualization in tinnitus.

As already mentioned above, gamma power spectra changes were observed after 1 Hz rTMS over the right TPJ. Although this effect disappears with a correction for multiple comparisons, this gamma observation could be of further relevance, in particular for treatment approaches, since activity in the gamma frequency range is supposed to be strongly connected with tinnitus perception (De Ridder et al., 2015a; van der Loo et al., 2009; Weisz et al., 2007b). Additional support comes from a previous TMS-EEG study showing decreased gamma band activity over right temporal regions after right frontal low frequency rTMS in tinnitus patients, whereas in healthy subjects gamma band activity was increased (Schecklmann et al., 2015).

In a broader view, these two gamma findings over parieto-occipital and temporal areas caused by right frontal respectively temporo-parietal low frequency rTMS, might support the notion of a widely spread cortical network involved in tinnitus as postulated by Schlee et al., (2009). Interestingly the authors report a cortical network comprised of frontal, temporal and parieto-occipital areas with functional alterations especially in the gamma frequency in line with the above-mentioned findings. Other research likewise emphasizes the involvement of other, non-auditory cortical regions as well, and suggests an existence of inter-individual network characteristics in tinnitus (Adjamian et al., 2014; Elgoyhen et al., 2015; Leaver et al., 2016).

As already mentioned by Schoisswohl et al. (2019a), there might be a prefrontal subtype in tinnitus patients, which preferably responds to prefrontal rTMS. An integration of prefrontal stimulation targets (De Ridder et al., 2013) next to temporal regions (Kreuzer et al., 2017) in future test sessions would be preferable to enable a systematic investigation of effect reliability as well as responder rates.

Since single session effects are often very small and difficult for the patients to evaluate, we opted to use an uncooled rTMS coil in study 4 to minimize the stimulation noise and account for potential confounding effects. Though, magnetic stimulations are accompanied by loud click sounds making it essential for patients to wear ear protection (Koponen et al., 2020). This

intensive rhythmic sound stimulation is suggested to potentially produce acoustic entrainment (Lorenz et al., 2010). Therefore, it is not clear if rTMS effects in tinnitus are caused by magnetic stimulations alone or by accompanied sound stimulations potentially inducing oscillatory entrainment or even RI. Prototypes of stimulation coils with decreased stimulation noise are under development and will hopefully be soon available in clinical research (Goetz et al., 2014; Peterchev et al., 2015). Such coils could facilitate completely new approaches in online adjustment of stimulation parameters as well as tinnitus loudness evaluations.

A common limitation of rTMS research, not only restricted to rTMS in tinnitus, is the determination of inhibitory or excitatory rTMS consequences caused by certain frequency protocols primary via motor cortex stimulations. According to Lorenz et al. (2010) it is not clear if insights from the motor cortex are equally valid for stimulations of other regions of the cortex. In view of brain state-dependent effects of rTMS (Siebner et al., 2004) along with pathological hyperactivity in the auditory cortex existing in tinnitus (Galazyuk et al., 2012), intended effects may shift or lack. As a matter of fact, intermittent theta burst stimulation, which is known to enhance motor cortex excitability, was found to produce inhibitory effects when applied over the temporal cortex (Lorenz et al., 2010). Further on it is not clear if stimulation intensity definition via motor cortex stimulations and subjects' RMTs can be effectively used for auditory cortex rTMS (Schoisswohl et al., 2019a). It was already proposed to determine the intensity for temporal rTMS via excitability measures of the auditory cortex (Meeus et al., 2009). This could, for example, be achieved with auditory evoked activity measurements (Lorenz et al., 2010; Zaehle et al., 2011).

Previous studies either used a specific sham coil (Eichhammer et al., 2003; Kleinjung et al., 2005; Langguth et al., 2014; Piccirillo et al., 2011) or tilted the coil away from the skull during active stimulation (Kreuzer et al., 2017; Landgrebe et al., 2017; Müller et al., 2013; Schecklmann et al., 2016) to facilitate placebo rTMS. In both cases rTMS-induced muscle contractions are not existent, hence patients stimulated might be aware of a placebo condition. In the both single session experiments at hand an active sham stimulation (0.1 Hz) was used, which is capable to induce muscle contractions and is suspected to not induce neuroplastic effects (Chen et al., 1997; Kumru et al., 2017). Superiority in short-term tinnitus suppression of verum rTMS in contrast to active sham was observed in the present thesis. Thus, this sham stimulation approach is recommended for future rTMS experiments in order to keep participants blinded. But there are hints that this type of sham protocol may affect other rTMS protocols with the potential to induce plasticity (Delvendahl et al., 2010a; Delvendahl et al., 2010b). A

significant progression of sham rTMS would be to mimic TMS-induced muscle contractions via electrical stimulation.

The most commonly used strategy to place the TMS coil for temporal stimulations in tinnitus is based on the 10-20 EEG system developed by Langguth et al. (2006). As new technologies in neuromodulation arrive, several rTMS trials employed neuronavigated rTMS in tinnitus (e.g., Hoekstra et al., 2013; Sahlsten et al., 2015, 2017; Schecklmann et al., 2016). In the present experiments a novel neuronavigation system with the possibility to control for the induced e-field was used as well. Stimulation positions were either defined in relation to Sahlsten et al. (2015, 2017) or via the 10-20 EEG system (CP5, CP6). Currently it is not clear if neuronavigated rTMS is superior to non-neuronavigated rTMS in tinnitus (Langguth et al., 2010; Sahlsten et al., 2019). This discrepancy could be attributed to the uncertainty about the correct stimulation targets/ positions of e.g., the auditory cortex. Personalization of temporal stimulation positions with respect to tonotopic map representations based on patients' tinnitus pitch (Sahlsten et al., 2017), patient-specific source localization of acoustic tinnitus suppression (analog to study 2) or definition of a functional "hot-spot" of auditory activity via resting state MRI might be suitable approaches.

Past research suggests that the BDNF represents the best predictor for response to non-invasive brain stimulation (Antal et al., 2010; Cheeran et al., 2008; Fidalgo et al., 2014; Polanía et al., 2018). Consequently, increases in BDNF polymorphisms should go together with an enhancement of neuroplastic effects caused by rTMS and result in a higher number of single session or treatment responders. Interestingly, recent investigations in the field of sports science show that physical training has the potential to increase the BDNF concentration in subjects' blood plasma (Nilsson et al., 2020). Parallel or pre rTMS physical activity might not only improve the quality of life and tinnitus severity (Carpenter-Thompson et al., 2015) but also enhance TMS responder rates in test sessions and treatment trials.

Overall, the present findings stress the idea that an individualization of rTMS might be a suitable approach to counteract the existing variability of rTMS effects. In view of the current literature, magnetic brain stimulation appears to be an extremely complex procedure with many degrees of freedom. Various technical (e.g., frequency, intensity) and physiological (e.g., brain state) parameters as well as their interdependency need to be considered and analyzed in more depth for optimal rTMS applications not only in tinnitus but also in other fields.

7.2. Best of both worlds

There is important evidence for the relevance of the intrinsic state of the brain before rTMS to be crucial for induced effect direction (Silvanto and Pascual-Leone, 2008). It was shown that transcranial direct current stimulation prior inhibitory low frequency rTMS is capable to reverse the intended consequences on motor cortex excitability (Siebner et al., 2004). Further, noise stimulations before temporal low frequency rTMS were similarly able to modulate auditory cortex excitability (Weisz et al., 2012). A combination of sound stimulation with transcranial direct current stimulation for the treatment of tinnitus has already been examined, showing inconclusive findings (Shekhawat et al., 2015; Teismann et al., 2014).

In the context of the present thesis, acoustic stimulation test sessions (study 1 and 2) and the identification of an individual superior sound stimulus for RI per patient can be combined with rTMS test sessions (study 3 and 4). Since it is not clear how different sound stimulations interact with different rTMS protocols, an inclusion of individual RI-stimuli in rTMS test session- same sound stimulation per patient before each rTMS protocols, might hypothetically alter the neural intrinsic state prior rTMS and enhance rTMS effects. Moreover, source localization of RI could provide a potential stimulation target for rTMS.

Alternatively, separated test sessions for acoustic stimulation response and rTMS response can be conducted to identify the best stimuli respectively protocol for short-term tinnitus suppression. Ultimately, these two can be combined to a personalized acoustic rTMS protocol.

7.3. Personalized treatments in tinnitus

Heterogeneity in tinnitus appearance among patients makes it rather difficult to find a general treatment option. Differences mainly occur in the dimensions tinnitus perception, causal risk factors, distress as well as treatment response plus various different comorbidities can be accompanied with the tinnitus percept. Therefor a development of a treatment for all “types” of tinnitus patients is rather unlikely emphasizing the need for treatment approaches which consider the individual patient (Cederroth et al., 2019).

Most research on personalized treatment approaches in tinnitus comes from sound therapy approaches, which customize stimuli according to the patients tinnitus characteristics. (e.g., Okamoto et al., 2010; Pantev et al., 2012) – considering the dimension tinnitus percept.

In the current thesis, the first two experiments are more or less associated to this field. The focus was to investigate the differences of personalized sound stimulations based on patients’ tinnitus characteristics (e.g., pitch, noise bandwidth or tinnitus loudness) for brief loudness suppression. A main limitation of such personalized sound interventions is their narrow focus on solely

tinnitus characteristics/ percept and not taking into account the tinnitus patient as a whole entity comprised of multiple factors involved in the perception of tinnitus as outlined above (Searchfield et al., 2017).

Another approach of treatment personalization is based on rTMS single sessions with different protocols as investigated in study 3 and 4 of the present thesis. Personalization of rTMS for short tinnitus loudness suppressions mainly focuses on the domain of response to a certain intervention but also partially accounts for subject-specific functional (different frequencies) and structural (definition of stimulation targets via individual anatomical scans) neurophysiological characteristics. The present experiments demonstrate the feasibility of this approach, but statistical superiority compared to a standard rTMS protocol is not yet provided (Kreuzer et al., 2017).

Both types of studies are limited in their narrow focus on only a certain dimension of tinnitus heterogeneity. Currently it is not obvious which tinnitus subtypes respond to which type of intervention. Essential groundwork for the personalization of tinnitus interventions comes from Simoes et al. (2019). The authors were able to identify a substantial number of factors relevant for a response to various interventions commonly used in tinnitus e.g., hearing aids, sound interventions or antidepressants. Interestingly, for rTMS response only laterality of hearing loss was identified as a significant predictor (Simoes et al. 2019). Current rTMS studies mainly focused on the laterality of tinnitus perception and not hearing loss. However, a study dedicated to expose predictors for rTMS failed to identify any (Lehner et al., 2012).

Personalization of tinnitus interventions constitutes a highly promising concept towards identification of a cure in the spirit of “What for Whom?!”. Future research taking into account a variety of dimensions in tinnitus heterogeneity as well as determining tinnitus patient subtypes, which are more probable to respond to a certain type of intervention, with big data approaches are highly needed.

7.4. Need for valid objective measurements

Tinnitus loudness assessments for used in the current thesis are premised on the subjective rating of tinnitus loudness changes after interventions. Attempts for an identification of objective tinnitus measurements or biomarkers range from research focusing on ongoing (Balkenhol et al., 2013; Lorenz et al., 2009; Pierzycki et al., 2016) or evoked (Cardon et al., 2020; Jacquemin et al., 2019; Paul et al., 2018) brain activity, functional near-infrared spectroscopy (Shoushtarian et al., 2020), neuroimaging (Liu et al., 2019) to physiological marker such as blood pressure or patients’ heart rate (Aydin and Searchfield, 2019). Currently

there is no valid objective way to measure tinnitus (Jackson et al., 2019). One of the aims of the present thesis was to examine neurophysiological correlates of transient acoustic tinnitus suppression (Schoisswohl et al., 2020b). In line with past observations, no correlation of behavioral and neural data was observed (Adjamian et al., 2012; Kahlbrock and Weisz, 2008; Pierzycki et al., 2016).

Pierzycki et al. (2016) even suggested to not use EEG as a biomarker for tinnitus. Though, contrasts of acoustic stimulation responder and non-responder in experiment 2 brought up differences in oscillatory brain activity in the alpha and gamma frequency range identical to differences between tinnitus patients and healthy subjects. Future neurophysiological studies in RI or other areas should keep track of this hint in systematical investigations in order to identify a valid neurophysiological marker for tinnitus suppression.

7.5. Further remarks

All experiments of the present thesis are subject to a common limitation, namely the unequitable gender distribution. From 101 tinnitus patients participating in the present experiments, only 27 (26.73%) participants were females. This gender ratio could be attributed to a higher prevalence of tinnitus in men compared to women (McCormack et al., 2016; Møller, 2011).

Recent work on gender differences reports, that females show higher tinnitus distress but also have more coping strategies than men (Fioretti et al., 2020; Niemann et al., 2020). Thus, it may be possible that men, even though women report higher distress, are more likely to seek professional help in dedicated tinnitus clinics causing unequal gender distributions in study samples. On the basis of differences in gender-specific treatment responses (Niemann et al., 2020; Van der Wal et al., 2020) and gender-differences in the ability to acoustically suppress the tinnitus percept (Hu et al., 2020), studies with balanced gender ratio are recommended.

Since the measures used for tinnitus loudness assessment are of a subjective nature plus the majority of the investigated tinnitus sample stated to experience tinnitus loudness fluctuations, the question arises if such evaluations are reliable. Data from two studies suggests that subjective assessments of tinnitus loudness (e.g., via VAS) constitute reliable measures (Adamchic Ilya et al., 2012; Zenner et al., 2005).

Nevertheless, it is important to identify objective measures or functional neurophysiological markers of tinnitus loudness alterations since loudness changes after short interventions are often quite small and difficult for patients to evaluate. Currently there is no clear evidence of a link between neural and behavioral data (Adjamian et al., 2014; Kahlbrock and Weisz, 2008; Pierzycki et al., 2016).

An important precondition for this, would be the reliability of neurophysiological measurements (e.g., resting state EEG) in the tinnitus population. Even though resting state measurements of spontaneous brain activity are reported as a reliable measure in healthy subjects (Gasser et al., 1985; Martín-Buro et al., 2016; McEvoy et al., 2000), there is currently no sufficient data for tinnitus. A single study was able to show test-retest reliability for whole scalp EEG power spectra in tinnitus (Pierzycki et al., 2016). Further test retest experiments with healthy subject contrasts are needed to make a clear statement about the reliability of neurophysiological measures in tinnitus.

7.6. Final conclusion

The purpose of the present thesis was to gain more profound insights behind the mechanisms of brief tinnitus suppression using personalized acoustic stimulations for RI induction as well as rTMS single sessions for assessment of test-retest reliability and personalization of magnetic stimulation protocols. Up to now, there is no overall treatment option for tinnitus on account of tinnitus heterogeneity. Individualization approaches as used in the present thesis potentially provide an appropriate way to overcome this issue. The significant findings emerged from these four experiments are differences in RI patterns between noise-like and tonal tinnitus patients and differences in tinnitus-associated spontaneous brain activity between acoustic stimulation responders and non-responders. Likewise, absence of test-retest reliability of rTMS effects and the feasibility of rTMS personalization via behavioral and electrophysiological responses were demonstrated. The observations and suggestions made in this thesis might provide essential indications and evidence points for future research attempts either in sound stimulation or rTMS and constitute an important next step *towards a moment of silence.*

8. References

Adamchic I, Toth T, Hauptmann C, Tass PA. Reversing pathologically increased EEG power by acoustic coordinated reset neuromodulation: Reversing Pathological Neural Activity in Tinnitus. Human Brain Mapping 2014;35:2099–118. https://doi.org/10.1002/hbm.22314.

Adamchic I, Toth T, Hauptmann C, Walger M, Langguth B, Klingmann I, et al. Acute effects and after-effects of acoustic coordinated reset neuromodulation in patients with chronic subjective tinnitus. NeuroImage: Clinical 2017;15:541–58. https://doi.org/10.1016/j.nicl.2017.05.017.

Adamchic Ilya, Langguth Berthold, Hauptmann Christian, Alexander Tass Peter. Psychometric Evaluation of Visual Analog Scale for the Assessment of Chronic Tinnitus. American Journal of Audiology 2012;21:215–25. https://doi.org/10.1044/1059-0889(2012/12-0010).

Adjamian P, Hall DA, Palmer AR, Allan TW, Langers DRM. Neuroanatomical abnormalities in chronic tinnitus in the human brain. Neurosci Biobehav Rev 2014;45:119–33. https://doi.org/10.1016/j.neubiorev.2014.05.013.

Adjamian P, Sereda M, Hall DA. The mechanisms of tinnitus: Perspectives from human functional neuroimaging. Hearing Research 2009;253:15–31. https://doi.org/10.1016/j.heares.2009.04.001.

Adjamian P, Sereda M, Zobay O, Hall DA, Palmer AR. Neuromagnetic Indicators of Tinnitus and Tinnitus Masking in Patients with and without Hearing Loss. Journal of the Association for Research in Otolaryngology 2012;13:715–31. https://doi.org/10.1007/s10162-012-0340-5.

Allen EA, Pasley BN, Duong T, Freeman RD. Transcranial magnetic stimulation elicits coupled neural and hemodynamic consequences. Science 2007;317:1918–21. https://doi.org/10.1126/science.1146426.

Antal A, Chaieb L, Moliadze V, Monte-Silva K, Poreisz C, Thirugnanasambandam N, et al. Brain-derived neurotrophic factor (BDNF) gene polymorphisms shape cortical plasticity in humans. Brain Stimulation 2010;3:230–7. https://doi.org/10.1016/j.brs.2009.12.003.

Ashton H, Reid K, Marsh R, Johnson I, Alter K, Griffiths T. High frequency localised “hot spots” in temporal lobes of patients with intractable tinnitus: A quantitative electroencephalographic (QEEG) study. Neuroscience Letters 2007;426:23–8. https://doi.org/10.1016/j.neulet.2007.08.034.

Aydin N, Searchfield GD. Changes in tinnitus and physiological biomarkers of stress in response to short-term broadband noise and sounds of nature. Complement Ther Med 2019;46:62–8. https://doi.org/10.1016/j.ctim.2019.07.018.

Aytac I, Baysal E, Gulsen S, Tumuklu K, Durucu C, Mumbuc LS, et al. Masking Treatment and its Effect on Tinnitus Parameters. Int Tinnitus J 2017;21:83–9. https://doi.org/10.5935/0946-5448.20170017.

Baguley D, McFerran D, Hall D. Tinnitus. The Lancet 2013;382:1600–7. https://doi.org/10.1016/S0140-6736(13)60142-7.

Balkenhol T, Wallhäusser-Franke E, Delb W. Psychoacoustic Tinnitus Loudness and Tinnitus-Related Distress Show Different Associations with Oscillatory Brain Activity. PLoS ONE 2013;8:e53180. https://doi.org/10.1371/journal.pone.0053180.

Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet 1985;1:1106–7.

Barozzi S, Ambrosetti U, Callaway SL, Behrens T, Passoni S, Bo LD. Effects of Tinnitus Retraining Therapy with Different Colours of Sound. The International Tinnitus Journal 2017;21. https://doi.org/10.5935/0946-5448.20170026.

Basile C-É, Fournier P, Hutchins S, Hébert S. Psychoacoustic Assessment to Improve Tinnitus Diagnosis. PLoS ONE 2013;8:e82995. https://doi.org/10.1371/journal.pone.0082995.

Bauer CA, Berry JL, Brozoski TJ. The effect of tinnitus retraining therapy on chronic tinnitus: A controlled trial: A Controlled Trial of Tinnitus Retraining Therapy. Laryngoscope Investigative Otolaryngology 2017;2:166–77. https://doi.org/10.1002/lio2.76.

Bilici S, Yigit O, Taskin U, Gor AP, Yilmaz ED. Medium-term results of combined treatment with transcranial magnetic stimulation and antidepressant drug for chronic tinnitus. Eur Arch Otorhinolaryngol 2015;272:337–43. https://doi.org/10.1007/s00405-013-2851-z.

Bläsing L, Goebel G, Flötzinger U, Berthold A, Kröner-Herwig B. Hypersensitivity to sound in tinnitus patients: an analysis of a construct based on questionnaire and audiological data. Int J Audiol 2010;49:518–26. https://doi.org/10.3109/14992021003724996.

Bradley MM, Lang PJ. Measuring emotion: The self-assessment manikin and the semantic differential. Journal of Behavior Therapy and Experimental Psychiatry 1994;25:49–59. https://doi.org/10.1016/0005-7916(94)90063-9.

Brainard DH. The Psychophysics Toolbox. Spatial Vision 1997;10:433–6. https://doi.org/10.1163/156856897X00357.

Buckley PF, Miller BJ. Personalized medicine for schizophrenia. NPJ Schizophr 2017;3. https://doi.org/10.1038/s41537-016-0001-5.

Cardon E, Joossen I, Vermeersch H, Jacquemin L, Mertens G, Vanderveken OM, et al. Systematic review and meta-analysis of late auditory evoked potentials as a candidate biomarker in the assessment of tinnitus. PLOS ONE 2020;15:e0243785. https://doi.org/10.1371/journal.pone.0243785.

Carpenter-Thompson JR, McAuley E, Husain FT. Physical Activity, Tinnitus Severity, and Improved Quality of Life. Ear and Hearing 2015;36:574–81. https://doi.org/10.1097/AUD.0000000000000169.

Cederroth CR, Gallus S, Hall DA, Kleinjung T, Langguth B, Maruotti A, et al. Editorial: Towards an Understanding of Tinnitus Heterogeneity. Front Aging Neurosci 2019;11. https://doi.org/10.3389/fnagi.2019.00053.

Cederroth CR, Lugo A, Edvall NK, Lazar A, Lopez-Escamez J-A, Bulla J, et al. Association between Hyperacusis and Tinnitus. J Clin Med 2020;9. https://doi.org/10.3390/jcm9082412.

Cheeran B, Talelli P, Mori F, Koch G, Suppa A, Edwards M, et al. A common polymorphism in the brain-derived neurotrophic factor gene (BDNF) modulates human cortical plasticity and the response to rTMS. J Physiol 2008;586:5717–25. https://doi.org/10.1113/jphysiol.2008.159905.

Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 1997;48:1398–403. https://doi.org/10.1212/wnl.48.5.1398.

Chervyakov AV, Chernyavsky AY, Sinitsyn DO, Piradov MA. Possible Mechanisms Underlying the Therapeutic Effects of Transcranial Magnetic Stimulation. Front Hum Neurosci 2015;9. https://doi.org/10.3389/fnhum.2015.00303.

Chung H-K, Tsai C-H, Lin Y-C, Chen J-M, Tsou Y-A, Wang C-Y, et al. Effectiveness of Theta-Burst Repetitive Transcranial Magnetic Stimulation for Treating Chronic Tinnitus. Audiology and Neurotology 2012;17:112–20. https://doi.org/10.1159/000330882.

Cima RFF, Maes IH, Joore MA, Scheyen DJWM, El Refaie A, Baguley DM, et al. Specialised treatment based on cognitive behaviour therapy versus usual care for tinnitus: a randomised controlled trial. Lancet 2012;379:1951–9. https://doi.org/10.1016/S0140-6736(12)60469-3.

Cima RFF, Mazurek B, Haider H, Kikidis D, Lapira A, Noreña A, et al. A multidisciplinary European guideline for tinnitus: diagnostics, assessment, and treatment. HNO 2019. https://doi.org/10.1007/s00106-019-0633-7.

Cocchi L, Zalesky A. Personalized Transcranial Magnetic Stimulation in Psychiatry. BPS: CNNI 2018;3:731–41. https://doi.org/10.1016/j.bpsc.2018.01.008.

Croenlein T, Langguth B, Pregler M, Kreuzer PM, Wetter TC, Schecklmann M. Insomnia in patients with chronic tinnitus: Cognitive and emotional distress as moderator variables. J Psychosom Res 2016;83:65–8. https://doi.org/10.1016/j.jpsychores.2016.03.001.

Crone NE, Boatman D, Gordon B, Hao L. Induced electrocorticographic gamma activity during auditory perception. Brazier Award-winning article, 2001. Clin Neurophysiol 2001;112:565–82. https://doi.org/10.1016/s1388-2457(00)00545-9.

Cuijpers P, Reynolds CF, Donker T, Li J, Andersson G, Beekman A. Personalized Treatment of Adult Depression: Medication, Psychotherapy, or Both? A Systematic Review. Depression and Anxiety 2012;29:855–64. https://doi.org/10.1002/da.21985.

De Ridder D, Congedo M, Vanneste S. The neural correlates of subjectively perceived and passively matched loudness perception in auditory phantom perception. Brain Behav 2015a;5. https://doi.org/10.1002/brb3.331.

De Ridder D, Elgoyhen AB, Romo R, Langguth B. Phantom percepts: Tinnitus and pain as persisting aversive memory networks. Proc Natl Acad Sci U S A 2011;108:8075–80. https://doi.org/10.1073/pnas.1018466108.

De Ridder D, van der Loo E, Van der Kelen K, Menovsky T, van de Heyning P, Moller A. Do tonic and burst TMS modulate the lemniscal and extralemniscal system differentially? Int J Med Sci 2007;4:242–6. https://doi.org/10.7150/ijms.4.242.

De Ridder D, Song J-J, Vanneste S. Frontal cortex TMS for tinnitus. Brain Stimul 2013;6:355–62. https://doi.org/10.1016/j.brs.2012.07.002.

De Ridder D, Vanneste S, Freeman W. The Bayesian brain: phantom percepts resolve sensory uncertainty. Neurosci Biobehav Rev 2014;44:4–15. https://doi.org/10.1016/j.neubiorev.2012.04.001.

De Ridder D, Vanneste S, Langguth B, Llinas R. Thalamocortical Dysrhythmia: A Theoretical Update in Tinnitus. Front Neurol 2015b;6. https://doi.org/10.3389/fneur.2015.00124.

De Ridder D, Verstraeten E, Van der Kelen K, De Mulder G, Sunaert S, Verlooy J, et al. Transcranial Magnetic Stimulation for Tinnitus: Influence of Tinnitus Duration on Stimulation Parameter Choice and Maximal Tinnitus Suppression: Otology & Neurotology 2005;26:616–9. https://doi.org/10.1097/01.mao.0000178146.91139.3c.

Deklerck Ann N., Degeest Sofie, Dhooge Ingeborg J. M., Keppler Hannah. Test–Retest Reproducibility of Response Duration in Tinnitus Patients With Positive Residual Inhibition. Journal of Speech, Language, and Hearing Research 2019;62:3531–44. https://doi.org/10.1044/2019_JSLHR-H-18-0514.

Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 2004;134:9–21. https://doi.org/10.1016/j.jneumeth.2003.10.009.

Delvendahl I., Jung N, Mainberger F, Mall V. Low-Frequency rTMS selectively modulates inhibitory intracortical networks. Neuropediatrics 2010a;41:V1258. https://doi.org/10.1055/s-0030-1265520.

Delvendahl I, Jung N, Mainberger F, Mall V. Occlusion of synaptic plasticity by gating. Klinische Neurophysiologie - KLIN NEUROPHYSIOL 2010b;41. https://doi.org/10.1055/s-0030-1250948.

Ding L, Shou G, Yuan H, Urbano D, Cha Y-H. Lasting modulation effects of rTMS on neural activity and connectivity as revealed by resting-state EEG. IEEE Trans Biomed Eng 2014;61:2070–80. https://doi.org/10.1109/TBME.2014.2313575.

Dohrmann K, Weisz N, Schlee W, Hartmann T, Elbert T. Neurofeedback for treating tinnitus. In: Langguth B, Hajak G, Kleinjung T, Cacace A, Møller AR, editors. Progress in Brain Research, vol. 166, Elsevier; 2007, p. 473–554. https://doi.org/10.1016/S0079-6123(07)66046-4.

Dong C, Chen C, Wang T, Gao C, Wang Y, Guan X, et al. Low-Frequency Repetitive Transcranial Magnetic Stimulation for the Treatment of Chronic Tinnitus: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Biomed Res Int 2020;2020:3141278. https://doi.org/10.1155/2020/3141278.

Draganova R, Ross B, Wollbrink A, Pantev C. Cortical steady-state responses to central and peripheral auditory beats. Cereb Cortex 2008;18:1193–200. https://doi.org/10.1093/cercor/bhm153.

Eggermont JJ. Pathophysiology of tinnitus. Prog Brain Res 2007;166:19–35. https://doi.org/10.1016/S0079-6123(07)66002-6.

Eggermont JJ, Roberts LE. The Neuroscience of Tinnitus: Understanding Abnormal and Normal Auditory Perception. Frontiers in Systems Neuroscience 2012;6. https://doi.org/10.3389/fnsys.2012.00053.

Eggermont JJ, Roberts LE. The neuroscience of tinnitus. Trends in Neurosciences 2004;27:676–82. https://doi.org/10.1016/j.tins.2004.08.010.

Eggermont JJ, Tass PA. Maladaptive Neural Synchrony in Tinnitus: Origin and Restoration. Frontiers in Neurology 2015;6. https://doi.org/10.3389/fneur.2015.00029.

Eichhammer P, Langguth B, Marienhagen J, Kleinjung T, Hajak G. Neuronavigated repetitive transcranial magnetic stimulation in patients with tinnitus: a short case series. Biological Psychiatry 2003;54:862–5. https://doi.org/10.1016/S0006-3223(02)01896-6.

Elgoyhen AB, Langguth B, De Ridder D, Vanneste S. Tinnitus: perspectives from human neuroimaging. Nature Reviews Neuroscience 2015;16:632–42. https://doi.org/10.1038/nrn4003.

Erlandsson S, Dauman N. Categorization of tinnitus in view of history and medical discourse. International Journal of Qualitative Studies on Health and Well-Being 2013;8:23530. https://doi.org/10.3402/qhw.v8i0.23530.

Farhadi M, Mahmoudian S, Saddadi F, Karimian AR, Mirzaee M, Ahmadizadeh M, et al. Functional brain abnormalities localized in 55 chronic tinnitus patients: fusion of SPECT coincidence imaging and MRI. J Cereb Blood Flow Metab 2010;30:864–70. https://doi.org/10.1038/jcbfm.2009.254.

Feldmann H. Time Patterns and Related Parameters in Masking of Tinnitus. Acta Oto-Laryngologica 1983;95:594–8. https://doi.org/10.3109/00016488309139449.

Feldmann H. Homolateral and contralateral masking of tinnitus by noise-bands and by pure tones. Audiology 1971;10:138–44.

Ferreira LM de BM, Ramos Júnior AN, Mendes EP. Characterization of tinnitus in the elderly and its possible related disorders. Braz J Otorhinolaryngol 2009;75:249–55.

Fidalgo TM, Morales-Quezada JL, Muzy GSC, Chiavetta NM, Mendonca ME, Santana MVB, et al. Biological markers in noninvasive brain stimulation trials in major depressive disorder: a systematic review. J ECT 2014;30:47–61. https://doi.org/10.1097/YCT.0b013e31828b34d8.

Fioretti A, Natalini E, Riedl D, Moschen R, Eibenstein A. Gender Comparison of Psychological Comorbidities in Tinnitus Patients – Results of a Cross-Sectional Study. Front Neurosci 2020;14. https://doi.org/10.3389/fnins.2020.00704.

Fitzgerald P. Intensity-dependent effects of 1 Hz rTMS on human corticospinal excitability. Clinical Neurophysiology 2002;113:1136–41. https://doi.org/10.1016/S1388-2457(02)00145-1.

Fitzgerald PB, Fountain S, Daskalakis ZJ. A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. Clinical Neurophysiology 2006;117:2584–96. https://doi.org/10.1016/j.clinph.2006.06.712.

Folmer RL. Lateralization of neural activity associated with tinnitus. Neuroradiology 2007;49:689–91; author reply 693-696. https://doi.org/10.1007/s00234-007-0255-8.

Folmer RL, Carroll JR, Rahim A, Shi Y, Hal Martin W. Effects of repetitive transcranial magnetic stimulation (rTMS) on chronic tinnitus. Acta Oto-Laryngologica 2006;126:96–101. https://doi.org/10.1080/03655230600895465.

Folmer RL, Theodoroff SM, Casiana L, Shi Y, Griest S, Vachhani J. Repetitive Transcranial Magnetic Stimulation Treatment for Chronic Tinnitus: A Randomized Clinical Trial. JAMA Otolaryngol Head Neck Surg 2015;141:716–22. https://doi.org/10.1001/jamaoto.2015.1219.

Forogh B, Yazdi-Bahri S-M, Ahadi T, Fereshtehnejad S-M, Raissi GR. Comparison of two protocols of transcranial magnetic stimulation for treatment of chronic tinnitus: a randomized controlled clinical trial of burst repetitive versus high-frequency repetitive Transcranial Magnetic Stimulation. Neurol Sci 2014;35:227–32. https://doi.org/10.1007/s10072-013-1487-5.

Fournier P, Cuvillier A-F, Gallego S, Paolino F, Paolino M, Quemar A, et al. A New Method for Assessing Masking and Residual Inhibition of Tinnitus. Trends Hear 2018;22. https://doi.org/10.1177/2331216518769996.

Fregni F, Marcondes R, Boggio PS, Marcolin MA, Rigonatti SP, Sanchez TG, et al. Transient tinnitus suppression induced by repetitive transcranial magnetic stimulation and transcranial direct current stimulation. European Journal of Neurology 2006;13:996–1001. https://doi.org/10.1111/j.1468-1331.2006.01414.x.

Fuller T, Cima R, Langguth B, Mazurek B, Vlaeyen JW, Hoare DJ. Cognitive behavioural therapy for tinnitus. Cochrane Database Syst Rev 2020;1:CD012614. https://doi.org/10.1002/14651858.CD012614.pub2.

Galazyuk AV, Longenecker RJ, Voytenko SV, Kristaponyte I, Nelson GL. Residual inhibition: From the putative mechanisms to potential tinnitus treatment. Hear Res 2019;375:1–13. https://doi.org/10.1016/j.heares.2019.01.022.

Galazyuk AV, Voytenko SV, Longenecker RJ. Long-Lasting forward Suppression of Spontaneous Firing in Auditory Neurons: Implication to the Residual Inhibition of Tinnitus. Journal of the Association for Research in Otolaryngology 2017;18:343–53. https://doi.org/10.1007/s10162-016-0601-9.

Galazyuk AV, Wenstrup JJ, Hamid MA. Tinnitus and underlying brain mechanisms. Curr Opin Otolaryngol Head Neck Surg 2012;20. https://doi.org/10.1097/MOO.0b013e3283577b81.

Gamboa OL, Antal A, Moliadze V, Paulus W. Simply longer is not better: reversal of theta burst after-effect with prolonged stimulation. Exp Brain Res 2010;204:181–7. https://doi.org/10.1007/s00221-010-2293-4.

Garnaat SL, Fukuda AM, Yuan S, Carpenter LL. Identification of clinical features and biomarkers that may inform a personalized approach to rTMS for depression. Personalized Medicine in Psychiatry 2019;17–18:4–16. https://doi.org/10.1016/j.pmip.2019.09.001.

Gasser T, Bächer P, Steinberg H. Test-retest reliability of spectral parameters of the EEG. Electroencephalography and Clinical Neurophysiology 1985;60:312–9. https://doi.org/10.1016/0013-4694(85)90005-7.

Genitsaridi E, Partyka M, Gallus S, Lopez-Escamez JA, Schecklmann M, Mielczarek M, et al. Standardised profiling for tinnitus research: The European School for Interdisciplinary Tinnitus Research Screening Questionnaire (ESIT-SQ). Hearing Research 2019;377:353–9. https://doi.org/10.1016/j.heares.2019.02.017.

Goebel G, Hiller W. [The tinnitus questionnaire. A standard instrument for grading the degree of tinnitus. Results of a multicenter study with the tinnitus questionnaire]. HNO 1994;42:166–72.

Goebel G, Langguth B, Scheffold J, Blasing L. Ein valides Screening-und Evaluationsinstrument zu Erfassung der Hyperakusisbelastung unter Beruecksichtigung von Phonophobie und Rekrutiment und Schwerhoerigkeit. Kongreß der Deutschen HNO-Gesellschaft, 2013, p. 154.

Goetz SM, Murphy DLK, Peterchev AV. Transcranial Magnetic Stimulation Device With Reduced Acoustic Noise. IEEE Magnetics Letters 2014;5:1–4. https://doi.org/10.1109/LMAG.2014.2351776.

Green DM. A maximum-likelihood method for estimating thresholds in a yes-no task. Journal of the Acoustical Society of America 1993;93:2096–105. https://doi.org/10.1121/1.406696.

Grewal R, Spielmann PM, Jones SEM, Hussain SSM. Clinical efficacy of tinnitus retraining therapy and cognitive behavioural therapy in the treatment of subjective tinnitus: a systematic review. The Journal of Laryngology & Otology 2014;128:1028–33. https://doi.org/10.1017/S0022215114002849.

Gross J, Kujala J, Hämäläinen M, Timmermann L, Schnitzler A, Salmelin R. Dynamic imaging of coherent sources: Studying neural interactions in the human brain. PNAS 2001;98:694–9. https://doi.org/10.1073/pnas.98.2.694.

Guerra A, López-Alonso V, Cheeran B, Suppa A. Variability in non-invasive brain stimulation studies: Reasons and results. Neuroscience Letters 2017;719:133330. https://doi.org/10.1016/j.neulet.2017.12.058.

Güntensperger D, Thüring C, Meyer M, Neff P, Kleinjung T. Neurofeedback for Tinnitus Treatment - Review and Current Concepts. Front Aging Neurosci 2017;9:386. https://doi.org/10.3389/fnagi.2017.00386.

Hafner A, Schoisswohl S, Simoes J, Schlee W, Schecklmann M, Langguth B, et al. Impact of personality on acoustic tinnitus suppression and emotional reaction to stimuli sounds. Progress in Brain Research, Elsevier; 2020. https://doi.org/10.1016/bs.pbr.2020.08.004.

Halawa I, Goldental A, Shirota Y, Kanter I, Paulus W. Less Might Be More: Conduction Failure as a Factor Possibly Limiting the Efficacy of Higher Frequencies in rTMS Protocols. Front Neurosci 2018;12:358. https://doi.org/10.3389/fnins.2018.00358.

Hall DA, Láinez MJ, Newman CW, Sanchez TG, Egler M, Tennigkeit F, et al. Treatment options for subjective tinnitus: Self reports from a sample of general practitioners and ENT physicians within Europe and the USA. BMC Health Serv Res 2011;11:302. https://doi.org/10.1186/1472-6963-11-302.

Hallam RS, Jakes SC, Hinchcliffe R. Cognitive variables in tinnitus annoyance. Br J Clin Psychol 1988;27 (Pt 3):213–22.

Hallett M. Transcranial Magnetic Stimulation: A Primer. Neuron 2007;55:187–99. https://doi.org/10.1016/j.neuron.2007.06.026.

Hallett M. Transcranial magnetic stimulation and the human brain. Nature 2000;406:147–50. https://doi.org/10.1038/35018000.

Harrison XA, Donaldson L, Correa-Cano ME, Evans J, Fisher DN, Goodwin CED, et al. A brief introduction to mixed effects modelling and multi-model inference in ecology. PeerJ 2018;6:e4794. https://doi.org/10.7717/peerj.4794.

Heller AJ. Classification and epidemiology of tinnitus. Otolaryngologic Clinics of North America 2003;36:239–48. https://doi.org/10.1016/S0030-6665(02)00160-3.

Henry JA, Frederick M, Sell S, Griest S, Abrams H. Validation of a novel combination hearing aid and tinnitus therapy device. Ear Hear 2015;36:42–52. https://doi.org/10.1097/AUD.0000000000000093.

Henry JA, Rheinsburg B, Zaugg T. Comparison of Custom Sounds for Achieving Tinnitus Relief. Journal of the American Academy of Audiology 2004;15:585–98. https://doi.org/10.3766/jaaa.15.8.6.

Henry JA, Roberts LE, Caspary DM, Theodoroff SM, Salvi RJ. Underlying Mechanisms of Tinnitus: Review and Clinical Implications. J Am Acad Audiol 2014;25:5–126. https://doi.org/10.3766/jaaa.25.1.2.

Henry JA, Roberts LE, Ellingson RM, Thielman EJ. Computer-Automated Tinnitus Assessment: Noise-Band Matching, Maskability, and Residual Inhibition. Journal of the American Academy of Audiology 2013;24:486–504. https://doi.org/10.3766/jaaa.24.6.5.

Hesse G. Evidence and evidence gaps in tinnitus therapy. GMS Current Topics in Otorhinolaryngology, Head and Neck Surgery 2016;15:Doc04. https://doi.org/10.3205/cto000131.

Hoare DJ, Searchfield GD, El Refaie A, Henry JA. Sound therapy for tinnitus management: practicable options. J Am Acad Audiol 2014;25:62–75. https://doi.org/10.3766/jaaa.25.1.5.

Hobson J, Chisholm E, El Refaie A. Sound therapy (masking) in the management of tinnitus in adults. Cochrane Database Syst Rev 2012;11:CD006371. https://doi.org/10.1002/14651858.CD006371.pub3.

Hoekstra CEL, Versnel H, Neggers SFW, Niesten MEF, van Zanten GA. Bilateral low-frequency repetitive transcranial magnetic stimulation of the auditory cortex in tinnitus patients is not effective: a randomised controlled trial. Audiol Neurootol 2013;18:362–73. https://doi.org/10.1159/000354977.

Hoffman RE, Cavus I. Slow transcranial magnetic stimulation, long-term depotentiation, and brain hyperexcitability disorders. Am J Psychiatry 2002;159:1093–102. https://doi.org/10.1176/appi.ajp.159.7.1093.

Holm S. A Simple Sequentially Rejective Multiple Test Procedure. Scandinavian Journal of Statistics 1979;6:65–70.

Hoogendam JM, Ramakers GMJ, Di Lazzaro V. Physiology of repetitive transcranial magnetic stimulation of the human brain. Brain Stimul 2010;3:95–118. https://doi.org/10.1016/j.brs.2009.10.005.

House JW, Brackmann DE. Tinnitus: surgical treatment. Ciba Found Symp 1981;85:204–16. https://doi.org/10.1002/9780470720677.ch12.

Hu S, Anschuetz L, Hall DA, Caversaccio M, Wimmer W. Susceptibility to Residual Inhibition is Associated with Hearing Loss and Tinnitus Chronicity. MedRxiv 2020. https://doi.org/10.1101/2020.08.05.20167346.

Hu S, Anschuetz L, Huth ME, Sznitman R, Blaser D, Kompis M, et al. Association Between Residual Inhibition and Neural Activity in Patients with Tinnitus: Protocol for a Controlled Within- and Between-Subject Comparison Study. JMIR Res Protoc 2019;8:e12270. https://doi.org/10.2196/12270.

Hui J, Tremblay S, Daskalakis ZJ. The Current and Future Potential of Transcranial Magnetic Stimulation With Electroencephalography in Psychiatry. Clinical Pharmacology & Therapeutics 2019;106:734–46. https://doi.org/10.1002/cpt.1541.

Hyvärinen P, Mendonça C, Santala O, Pulkki V, Aarnisalo AA. Auditory localization by subjects with unilateral tinnitus. J Acoust Soc Am 2016;139:2280. https://doi.org/10.1121/1.4946897.

Jackson R, Vijendren A, Phillips J. Objective Measures of Tinnitus: a Systematic Review. Otology & Neurotology 2019;40:154–63. https://doi.org/10.1097/MAO.0000000000002116.

Jacquemin L, Mertens G, Van de Heyning P, Vanderveken OM, Topsakal V, De Hertogh W, et al. An Exploratory Study on the Use of Event-Related Potentials as an Objective Measure of Auditory Processing and Therapy Effect in Patients With Tinnitus: A Transcranial Direct Current Stimulation Study. Otol Neurotol 2019;40:e868–75. https://doi.org/10.1097/MAO.0000000000002380.

Jagoda L, Giroud N, Neff P, Kegel A, Kleinjung T, Meyer M. Speech perception in tinnitus is related to individual distress level - A neurophysiological study. Hear Res 2018;367:48–58. https://doi.org/10.1016/j.heares.2018.07.001.

Jastreboff PJ. 25 Years of tinnitus retraining therapy. HNO 2015;63:307–11. https://doi.org/10.1007/s00106-014-2979-1.

Jastreboff PJ. Phantom auditory perception (tinnitus): mechanisms of generation and perception. Neuroscience Research 1990;8:221–54. https://doi.org/10.1016/0168-0102(90)90031-9.

Joliot M, Ribary U, Llinás R. Human oscillatory brain activity near 40 Hz coexists with cognitive temporal binding. Proc Natl Acad Sci USA 1994;91:11748–51. https://doi.org/10.1073/pnas.91.24.11748.

Kahlbrock N, Weisz N. Transient reduction of tinnitus intensity is marked by concomitant reductions of delta band power. BMC Biology 2008;6:4. https://doi.org/10.1186/1741-7007-6-4.

Khedr EM, Abo-Elfetoh N, Rothwell JC, El-Atar A, Sayed E, Khalifa H. Contralateral versus ipsilateral rTMS of temporoparietal cortex for the treatment of chronic unilateral tinnitus: comparative study. Eur J Neurol 2010;17:976–83. https://doi.org/10.1111/j.1468-1331.2010.02965.x.

Khedr EM, Rothwell JC, Ahmed MA, El-Atar A. Effect of daily repetitive transcranial magnetic stimulation for treatment of tinnitus: comparison of different stimulus frequencies. J Neurol Neurosurg Psychiatry 2008;79:212–5. https://doi.org/10.1136/jnnp.2007.127712.

King ROC, Singh Shekhawat G, King C, Chan E, Kobayashi K, Searchfield GD. The Effect of Auditory Residual Inhibition on Tinnitus and the Electroencephalogram. Ear and Hearing 2020;Publish Ahead of Print. https://doi.org/10.1097/AUD.0000000000000907.

Kleiner M, Brainard D, Pelli D, Ingling A, Murray R, Broussard C. What's new in psychtoolbox-3. Perception 2007;36:1–16.

Kleinjung T, Eichhammer P, Landgrebe M, Sand P, Hajak G, Steffens T, et al. Combined temporal and prefrontal transcranial magnetic stimulation for tinnitus treatment: a pilot study. Otolaryngol Head Neck Surg 2008;138:497–501. https://doi.org/10.1016/j.otohns.2007.12.022.

Kleinjung T, Eichhammer P, Langguth B, Jacob P, Marienhagen J, Hajak G, et al. Long-term effects of repetitive transcranial magnetic stimulation (rTMS) in patients with chronic tinnitus. Otolaryngol Head Neck Surg 2005;132:566–9. https://doi.org/10.1016/j.otohns.2004.09.134.

Kleinjung T, Fischer B, Langguth B, Sand PG, Hajak G, Dvorakova J, et al. Validierung einer deutschsprachigen Version des „Tinnitus Handicap Inventory". Psychiat Prax 2007a;34:S140–2. https://doi.org/10.1055/s-2006-940218.

Kleinjung T, Langguth B. Avenue for Future Tinnitus Treatments. Otolaryngol Clin North Am 2020;53:667–83. https://doi.org/10.1016/j.otc.2020.03.013.

Kleinjung T, Steffens T, Landgrebe M, Vielsmeier V, Frank E, Burger J, et al. Repetitive transcranial magnetic stimulation for tinnitus treatment: no enhancement by the dopamine and noradrenaline reuptake inhibitor bupropion. Brain Stimul 2011;4:65–70. https://doi.org/10.1016/j.brs.2010.03.007.

Kleinjung T, Steffens T, Landgrebe M, Vielsmeier V, Frank E, Hajak G, et al. Levodopa does not enhance the effect of low-frequency repetitive transcranial magnetic stimulation in tinnitus treatment. Otolaryngol Head Neck Surg 2009;140:92–5. https://doi.org/10.1016/j.otohns.2008.10.007.

Kleinjung T, Steffens T, Sand P, Murthum T, Hajak G, Strutz J, et al. Which tinnitus patients benefit from transcranial magnetic stimulation? Otolaryngol Head Neck Surg 2007b;137:589–95. https://doi.org/10.1016/j.otohns.2006.12.007.

Klimesch W, Sauseng P, Hanslmayr S. EEG alpha oscillations: the inhibition-timing hypothesis. Brain Res Rev 2007;53:63–88. https://doi.org/10.1016/j.brainresrev.2006.06.003.

Klomjai W, Katz R, Lackmy-Vallée A. Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). Annals of Physical and Rehabilitation Medicine 2015;58:208–13. https://doi.org/10.1016/j.rehab.2015.05.005.

Kohrman D, Wan G, Cassinotti L, Corfas G. Hidden hearing loss, a disorder with multiple etiologies and mechanisms. Cold Spring Harb Perspect Med 2020;10. https://doi.org/10.1101/cshperspect.a035493.

Koponen LM, Goetz SM, Tucci DL, Peterchev AV. Sound comparison of seven TMS coils at matched stimulation strength. Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation 2020;13:873–80. https://doi.org/10.1016/j.brs.2020.03.004.

Kreuzer PM, Landgrebe M, Schecklmann M, Poeppl TB, Vielsmeier V, Hajak G, et al. Can Temporal Repetitive Transcranial Magnetic Stimulation be Enhanced by Targeting Affective Components of Tinnitus with Frontal rTMS? A Randomized Controlled Pilot Trial. Front Syst Neurosci 2011;5:88. https://doi.org/10.3389/fnsys.2011.00088.

Kreuzer PM, Poeppl TB, Bulla J, Schlee W, Lehner A, Langguth B, et al. A proof-of-concept study on the combination of repetitive transcranial magnetic stimulation and relaxation techniques in chronic tinnitus. J Neural Transm (Vienna) 2016;123:1147–57. https://doi.org/10.1007/s00702-016-1588-4.

Kreuzer PM, Poeppl TB, Rupprecht R, Vielsmeier V, Lehner A, Langguth B, et al. Individualized Repetitive Transcranial Magnetic Stimulation Treatment in Chronic Tinnitus? Front Neurol 2017;8:126. https://doi.org/10.3389/fneur.2017.00126.

Kristeva-Feige R, Feige B, Kowalik Z, Ross B. Neuromagnetic activity during residual inhibition in tinnitus. Journal of Audiological Medicine 1995;4:135–42.

Kumru H, Albu S, Rothwell J, Leon D, Flores C, Opisso E, et al. Modulation of motor cortex excitability by paired peripheral and transcranial magnetic stimulation. Clinical Neurophysiology 2017;128:2043–7. https://doi.org/10.1016/j.clinph.2017.06.041.

Lan L, Li J, Chen Yanhong, Chen W, Li W, Zhao F, et al. Alterations of brain activity and functional connectivity in transition from acute to chronic tinnitus. Human Brain Mapping 2021;42:485–94. https://doi.org/10.1002/hbm.25238.

Landgrebe M, Hajak G, Wolf S, Padberg F, Klupp P, Fallgatter AJ, et al. 1-Hz rTMS in the treatment of tinnitus: A sham-controlled, randomized multicenter trial. Brain Stimul 2017;10:1112–20. https://doi.org/10.1016/j.brs.2017.08.001.

Landry EC, Sandoval XCR, Simeone CN, Tidball G, Lea J, Westerberg BD. Systematic Review and Network Meta-analysis of Cognitive and/or Behavioral Therapies (CBT) for Tinnitus. Otol Neurotol 2020;41:153–66. https://doi.org/10.1097/MAO.0000000000002472.

Langguth B. Non-Invasive Neuromodulation for Tinnitus. J Audiol Otol 2020;24:113–8. https://doi.org/10.7874/jao.2020.00052.

Langguth B, Eichhammer P, Kreutzer A, Maenner P, Marienhagen J, Kleinjung T, et al. The impact of auditory cortex activity on characterizing and treating patients with chronic tinnitus--first results from a PET study. Acta Otolaryngol Suppl 2006a:84–8. https://doi.org/10.1080/03655230600895317.

Langguth B, Eichhammer P, Wiegand R, Marienhegen J, Maenner P, Jacob P, et al. Neuronavigated rTMS in a patient with chronic tinnitus. Effects of 4 weeks treatment. Neuroreport 2003;14:977–80. https://doi.org/10.1097/01.wnr.0000068897.39523.41.

Langguth B, Elgoyhen AB, Cederroth CR. Therapeutic Approaches to the Treatment of Tinnitus. Annu Rev Pharmacol Toxicol 2019;59:291–313. https://doi.org/10.1146/annurev-pharmtox-010818-021556.

Langguth B, Goodey R, Azevedo A, Bjorne A, Cacace A, Crocetti A, et al. Consensus for tinnitus patient assessment and treatment outcome measurement: Tinnitus Research Initiative meeting, Regensburg, July 2006. Prog Brain Res 2007;166:525–36. https://doi.org/10.1016/S0079-6123(07)66050-6.

Langguth B, Kleinjung T, Frank E, Landgrebe M, Sand P, Dvorakova J, et al. High-frequency priming stimulation does not enhance the effect of low-frequency rTMS in the treatment of tinnitus. Exp Brain Res 2008;184:587–91. https://doi.org/10.1007/s00221-007-1228-1.

Langguth B, Kleinjung T, Landgrebe M, de Ridder D, Hajak G. rTMS for the treatment of tinnitus: The role of neuronavigation for coil positioning. Neurophysiologie Clinique/Clinical Neurophysiology 2010;40:45–58. https://doi.org/10.1016/j.neucli.2009.03.001.

Langguth B, Kreuzer PM, Kleinjung T, De Ridder D. Tinnitus: causes and clinical management. The Lancet Neurology 2013;12:920–30. https://doi.org/10.1016/S1474-4422(13)70160-1.

Langguth B, Landgrebe M, Frank E, Schecklmann M, Sand PG, Vielsmeier V, et al. Efficacy of different protocols of transcranial magnetic stimulation for the treatment of tinnitus: Pooled analysis of two randomized controlled studies. World J Biol Psychiatry 2014;15:276–85. https://doi.org/10.3109/15622975.2012.708438.

Langguth B, Zowe M, Landgrebe M, Sand P, Kleinjung T, Binder H, et al. Transcranial Magnetic Stimulation for the Treatment of Tinnitus: A New Coil Positioning Method and First Results. Brain Topography 2006b;18:241–7. https://doi.org/10.1007/s10548-006-0002-1.

Lanting CP, de Kleine E, van Dijk P. Neural activity underlying tinnitus generation: results from PET and fMRI. Hear Res 2009;255:1–13. https://doi.org/10.1016/j.heares.2009.06.009.

Leaver AM, Turesky TK, Seydell-Greenwald A, Morgan S, Kim HJ, Rauschecker JP. Intrinsic network activity in tinnitus investigated using functional MRI. Human Brain Mapping 2016;37:2717–35. https://doi.org/10.1002/hbm.23204.

Lee S-Y, Choi BY, Koo J-W, De Ridder D, Song J-J. Cortical Oscillatory Signatures Reveal the Prerequisites for Tinnitus Perception: A Comparison of Subjects With Sudden Sensorineural Hearing Loss With and Without Tinnitus. Front Neurosci 2020;14. https://doi.org/10.3389/fnins.2020.596647.

Lefaucheur J-P, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018). Clinical Neurophysiology 2020;131:474–528. https://doi.org/10.1016/j.clinph.2019.11.002.

Lefaucheur J-P, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clinical Neurophysiology 2014;125:2150–206. https://doi.org/10.1016/j.clinph.2014.05.021.

Lefebvre-Demers M, Doyon N, Fecteau S. Non-invasive neuromodulation for tinnitus: a meta-analysis and modeling studies. Brain Stimul 2020. https://doi.org/10.1016/j.brs.2020.11.014.

Lehner A, Schecklmann M, Greenlee MW, Rupprecht R, Langguth B. Triple-site rTMS for the treatment of chronic tinnitus: a randomized controlled trial. Sci Rep 2016;6:22302. https://doi.org/10.1038/srep22302.

Lehner A, Schecklmann M, Landgrebe M, Kreuzer PM, Poeppl TB, Frank E, et al. Predictors for rTMS response in chronic tinnitus. Front Syst Neurosci 2012;6:11. https://doi.org/10.3389/fnsys.2012.00011.

Lehner A, Schecklmann M, Poeppl TB, Kreuzer PM, Peytard J, Frank E, et al. Efficacy and Safety of Repeated Courses of rTMS Treatment in Patients with Chronic Subjective Tinnitus. Biomed Res Int 2015;2015:975808. https://doi.org/10.1155/2015/975808.

Lehner A, Schecklmann M, Poeppl TB, Kreuzer PM, Vielsmeier V, Rupprecht R, et al. Multisite rTMS for the treatment of chronic tinnitus: stimulation of the cortical tinnitus network--a pilot study. Brain Topogr 2013;26:501–10. https://doi.org/10.1007/s10548-012-0268-4.

Leiner DJ. SoSci Survey. 2016.

Lerner AJ, Wassermann EM, Tamir DI. Seizures from transcranial magnetic stimulation 2012-2016: Results of a survey of active laboratories and clinics. Clin Neurophysiol 2019. https://doi.org/10.1016/j.clinph.2019.03.016.

Li J, Jin J, Xi S, Zhu Q, Chen Y, Huang M, et al. Clinical efficacy of cognitive behavioral therapy for chronic subjective tinnitus. Am J Otolaryngol 2019;40:253–6. https://doi.org/10.1016/j.amjoto.2018.10.017.

Li LP-H, Shiao A-S, Li C-T, Lee P-L, Cheng C-M, Chou C-C, et al. Steady-state auditory evoked fields reflect long-term effects of repetitive transcranial magnetic stimulation in tinnitus. Clinical Neurophysiology 2019;130:1665–72. https://doi.org/10.1016/j.clinph.2019.05.022.

Liu Y, Niu H, Zhu J, Zhao P, Yin H, Ding H, et al. Morphological Neuroimaging Biomarkers for Tinnitus: Evidence Obtained by Applying Machine Learning. Neural Plast 2019;2019. https://doi.org/10.1155/2019/1712342.

Llinás R, Urbano FJ, Leznik E, Ramírez RR, van Marle HJF. Rhythmic and dysrhythmic thalamocortical dynamics: GABA systems and the edge effect. Trends Neurosci 2005;28:325–33. https://doi.org/10.1016/j.tins.2005.04.006.

Llinás RR, Ribary U, Jeanmonod D, Kronberg E, Mitra PP. Thalamocortical dysrhythmia: A neurological and neuropsychiatric syndrome characterized by magnetoencephalography. Proc Natl Acad Sci USA 1999;96:15222–7. https://doi.org/10.1073/pnas.96.26.15222.

Londero A, Bonfils P, Lefaucheur JP. Transcranial magnetic stimulation and subjective tinnitus. A review of the literature, 2014–2016. European Annals of Otorhinolaryngology, Head and Neck Diseases 2018;135:51–8. https://doi.org/10.1016/j.anorl.2017.12.001.

van der Loo E, Gais S, Congedo M, Vanneste S, Plazier M, Menovsky T, et al. Tinnitus intensity dependent gamma oscillations of the contralateral auditory cortex. PLoS ONE 2009;4:e7396. https://doi.org/10.1371/journal.pone.0007396.

López-Alonso V, Cheeran B, Río-Rodríguez D, Fernández-del-Olmo M. Inter-individual Variability in Response to Non-invasive Brain Stimulation Paradigms. Brain Stimulation 2014;7:372–80. https://doi.org/10.1016/j.brs.2014.02.004.

Lorenz I, Müller N, Schlee W, Hartmann T, Weisz N. Loss of alpha power is related to increased gamma synchronization-A marker of reduced inhibition in tinnitus? Neurosci Lett 2009;453:225–8. https://doi.org/10.1016/j.neulet.2009.02.028.

Lorenz I, Müller N, Schlee W, Langguth B, Weisz N. Short-Term Effects of Single Repetitive TMS Sessions on Auditory Evoked Activity in Patients With Chronic Tinnitus. Journal of Neurophysiology 2010;104:1497–505. https://doi.org/10.1152/jn.00370.2010.

Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A. Interindividual variability of the modulatory effects of repetitive transcranial magnetic stimulation on cortical excitability. Exp Brain Res 2000;133:425–30. https://doi.org/10.1007/s002210000432.

Martín-Buro MC, Garcés P, Maestú F. Test-retest reliability of resting-state magnetoencephalography power in sensor and source space. Human Brain Mapping 2016;37:179–90. https://doi.org/10.1002/hbm.23027.

Mazurek B, Olze H, Haupt H, Szczepek AJ. The More the Worse: the Grade of Noise-Induced Hearing Loss Associates with the Severity of Tinnitus. International Journal of Environmental Research and Public Health 2010;7:3071–9. https://doi.org/10.3390/ijerph7083071.

McCormack A, Edmondson-Jones M, Somerset S, Hall D. A systematic review of the reporting of tinnitus prevalence and severity. Hearing Research 2016;337:70–9. https://doi.org/10.1016/j.heares.2016.05.009.

McEvoy LK, Smith ME, Gevins A. Test–retest reliability of cognitive EEG. Clinical Neurophysiology 2000;111:457–63. https://doi.org/10.1016/S1388-2457(99)00258-8.

Meeus O, Blaivie C, Ost J, De Ridder D, Van de Heyning P. Influence of Tonic and Burst Transcranial Magnetic Stimulation Characteristics on Acute Inhibition of Subjective Tinnitus: Otology & Neurotology 2009;30:697–703. https://doi.org/10.1097/MAO.0b013e3181b05023.

Meyer M, Luethi MS, Neff P, Langer N, Büchi S. Disentangling Tinnitus Distress and Tinnitus Presence by Means of EEG Power Analysis. Neural Plast 2014;2014. https://doi.org/10.1155/2014/468546.

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

Mohan A, De Ridder D, Vanneste S. Graph theoretical analysis of brain connectivity in phantom sound perception. Scientific Reports 2016;6:19683. https://doi.org/10.1038/srep19683.

Møller AR. Epidemiology of Tinnitus in Adults. In: Møller AR, Langguth B, De Ridder D, Kleinjung T, editors. Textbook of Tinnitus, New York, NY: Springer; 2011, p. 29–37. https://doi.org/10.1007/978-1-60761-145-5_5.

Møller AR. Tinnitus: presence and future. Prog Brain Res 2007;166:3–16. https://doi.org/10.1016/S0079-6123(07)66001-4.

Møller AR. Neural plasticity in tinnitus. Prog Brain Res 2006;157:365–72. https://doi.org/10.1016/S0079-6123(06)57022-0.

Moore DR, Zobay O, Mackinnon RC, Whitmer WM, Akeroyd MA. Lifetime leisure music exposure associated with increased frequency of tinnitus. Hear Res 2017;347:18–27. https://doi.org/10.1016/j.heares.2016.10.030.

Mühlnickel W, Elbert T, Taub E, Flor H. Reorganization of auditory cortex in tinnitus. PNAS 1998;95:10340–3. https://doi.org/10.1073/pnas.95.17.10340.

Müller N, Lorenz I, Langguth B, Weisz N. rTMS induced tinnitus relief is related to an increase in auditory cortical alpha activity. PLoS One 2013;8:e55557. https://doi.org/10.1371/journal.pone.0055557.

Nakagawa S, Johnson PCD, Schielzeth H. The coefficient of determination R2 and intra-class correlation coefficient from generalized linear mixed-effects models revisited and expanded. J R Soc Interface 2017;14. https://doi.org/10.1098/rsif.2017.0213.

Neff P, Hemsley C, Kraxner F, Weidt S, Kleinjung T, Meyer M. Active listening to tinnitus and its relation to resting state EEG activity. Neuroscience Letters 2019a;694:176–83. https://doi.org/10.1016/j.neulet.2018.11.008.

Neff P, Michels J, Meyer M, Schecklmann M, Langguth B, Schlee W. 10 Hz Amplitude Modulated Sounds Induce Short-Term Tinnitus Suppression. Frontiers in Aging Neuroscience 2017;9. https://doi.org/10.3389/fnagi.2017.00130.

Neff P, Zielonka L, Meyer M, Langguth B, Schecklmann M, Schlee W. Comparison of Amplitude Modulated Sounds and Pure Tones at the Tinnitus Frequency: Residual Tinnitus Suppression and Stimulus Evaluation. Trends in Hearing 2019b;23:2331216519833841. https://doi.org/10.1177/2331216519833841.

Nettekoven C, Volz LJ, Kutscha M, Pool E-M, Rehme AK, Eickhoff SB, et al. Dose-dependent effects of theta burst rTMS on cortical excitability and resting-state connectivity of the human motor system. J Neurosci 2014;34:6849–59. https://doi.org/10.1523/JNEUROSCI.4993-13.2014.

Nettekoven C, Volz LJ, Leimbach M, Pool E-M, Rehme AK, Eickhoff SB, et al. Inter-individual variability in cortical excitability and motor network connectivity following multiple blocks of rTMS. NeuroImage 2015;118:209–18. https://doi.org/10.1016/j.neuroimage.2015.06.004.

Newman CW, Jacobson GP, Spitzer JB. Development of the Tinnitus Handicap Inventory. Arch Otolaryngol Head Neck Surg 1996;122:143–8. https://doi.org/10.1001/archotol.1996.01890140029007.

Niemann U, Boecking B, Brüggemann P, Mazurek B, Spiliopoulou M. Gender-Specific Differences in Patients With Chronic Tinnitus—Baseline Characteristics and Treatment Effects. Frontiers in Neuroscience 2020;14. https://doi.org/10.3389/fnins.2020.00487.

Nilsson J, Ekblom Ö, Ekblom M, Lebedev A, Tarassova O, Moberg M, et al. Acute increases in brain-derived neurotrophic factor in plasma following physical exercise relates to subsequent learning in older adults. Scientific Reports 2020;10:4395. https://doi.org/10.1038/s41598-020-60124-0.

Noda Y. Toward the establishment of neurophysiological indicators for neuropsychiatric disorders using transcranial magnetic stimulation-evoked potentials: A systematic review. Psychiatry Clin Neurosci 2020;74:12–34. https://doi.org/10.1111/pcn.12936.

Noh T-S, Kyong JS, Chang MY, Park M-K, Lee J-H, Oh S-H, et al. 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. Otol Neurotol 2017;38:296–303. https://doi.org/10.1097/MAO.0000000000001266.

Noh T-S, Kyong J-S, Park MK, Lee JH, Oh SH, Chung CK, et al. Treatment Outcome of Auditory and Frontal Dual-Site rTMS in Tinnitus Patients and Changes in Magnetoencephalographic Functional Connectivity after rTMS: Double-Blind Randomized Controlled Trial. AUD 2019:1–6. https://doi.org/10.1159/000503134.

Noh T-S, Kyong J-S, Park MK, Lee JH, Oh SH, Suh M-W. Dual-site rTMS is More Effective than Single-site rTMS in Tinnitus Patients: A Blinded Randomized Controlled Trial. Brain Topogr 2020;33:767–75. https://doi.org/10.1007/s10548-020-00797-y.

Nondahl DM, Cruickshanks KJ, Dalton DS, Klein BEK, Klein R, Schubert CR, et al. The impact of tinnitus on quality of life in older adults. J Am Acad Audiol 2007;18:257–66. https://doi.org/10.3766/jaaa.18.3.7.

Nondahl DM, Cruickshanks KJ, Huang G-H, Klein BE, Klein R, Nieto FJ, et al. Tinnitus and its Risk Factors in the Beaver Dam Offspring Study. Int J Audiol 2011;50:313–20. https://doi.org/10.3109/14992027.2010.551220.

Norena A, Micheyl C, Chéry-Croze S, Collet L. Psychoacoustic Characterization of the Tinnitus Spectrum: Implications for the Underlying Mechanisms of Tinnitus. Audiology and Neurotology 2002;7:358–69. https://doi.org/10.1159/000066156.

Noreña AJ, Eggermont JJ. Enriched acoustic environment after noise trauma abolishes neural signs of tinnitus. NeuroReport 2006;17:559–63.

Okamoto H, Stracke H, Stoll W, Pantev C. Listening to tailor-made notched music reduces tinnitus loudness and tinnitus-related auditory cortex activity. Proceedings of the National Academy of Sciences 2010;107:1207–10. https://doi.org/10.1073/pnas.0911268107.

Oostenveld R, Fries P, Maris E, Schoffelen J-M. FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data. Computational Intelligence and Neuroscience 2011;2011:1–9. https://doi.org/10.1155/2011/156869.

Oostenveld R, Stegeman DF, Praamstra P, van Oosterom A. Brain symmetry and topographic analysis of lateralized event-related potentials. Clinical Neurophysiology 2003;114:1194–202. https://doi.org/10.1016/S1388-2457(03)00059-2.

Padberg F, Zwanzger P, Keck ME, Kathmann N, Mikhaiel P, Ella R, et al. Repetitive Transcranial Magnetic Stimulation (rTMS) in Major Depression: Relation between Efficacy and Stimulation Intensity. Neuropsychopharmacology 2002;27:638–45. https://doi.org/10.1016/S0893-133X(02)00338-X.

Pantev C, Okamoto H, Teismann H. Music-induced cortical plasticity and lateral inhibition in the human auditory cortex as foundations for tonal tinnitus treatment. Frontiers in Systems Neuroscience 2012;6. https://doi.org/10.3389/fnsys.2012.00050.

Pascual-Leone A, Valls-Solé J, Wassermann EM, Hallett M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain 1994;117 (Pt 4):847–58.

Pattyn T, Van Den Eede F, Vanneste S, Cassiers L, Veltman DJ, Van De Heyning P, et al. Tinnitus and anxiety disorders: A review. Hearing Research 2016;333:255–65. https://doi.org/10.1016/j.heares.2015.08.014.

Paul BT, Schoenwiesner M, Hébert S. Towards an objective test of chronic tinnitus: Properties of auditory cortical potentials evoked by silent gaps in tinnitus-like sounds. Hear Res 2018;366:90–8. https://doi.org/10.1016/j.heares.2018.04.005.

Perrin F, Pernier J, Bertrand O, Echallier JF. Spherical splines for scalp potential and current density mapping. Electroencephalography and Clinical Neurophysiology 1989;72:184–7. https://doi.org/10.1016/0013-4694(89)90180-6.

Peter N, Liyanage N, Pfiffner F, Huber A, Kleinjung T. The Influence of Cochlear Implantation on Tinnitus in Patients with Single-Sided Deafness: A Systematic Review. Otolaryngol Head Neck Surg 2019;161:576–88. https://doi.org/10.1177/0194599819846084.

Peterchev AV, Murphy DLK, Goetz SM. Quiet transcranial magnetic stimulation: Status and future directions. Annu Int Conf IEEE Eng Med Biol Soc 2015;2015:226–9. https://doi.org/10.1109/EMBC.2015.7318341.

Peters H, Shao J, Scherr M, Schwerthöffer D, Zimmer C, Förstl H, et al. More Consistently Altered Connectivity Patterns for Cerebellum and Medial Temporal Lobes than for Amygdala and Striatum in Schizophrenia. Front Hum Neurosci 2016;10. https://doi.org/10.3389/fnhum.2016.00055.

Piccirillo JF, Garcia KS, Nicklaus J, Pierce K, Burton H, Vlassenko AG, et al. Low-frequency repetitive transcranial magnetic stimulation to the temporoparietal junction for tinnitus. Arch Otolaryngol Head Neck Surg 2011;137:221–8. https://doi.org/10.1001/archoto.2011.3.

Picton TW, John MS, Dimitrijevic A, Purcell D. Human auditory steady-state responses. Int J Audiol 2003;42:177–219.

Pierzycki RH, McNamara AJ, Hoare DJ, Hall DA. Whole scalp resting state EEG of oscillatory brain activity shows no parametric relationship with psychoacoustic and psychosocial assessment of tinnitus: A repeated measures study. Hearing Research 2016;331:101–8. https://doi.org/10.1016/j.heares.2015.11.003.

Plewnia C, Bartels M, Gerloff C. Transient suppression of tinnitus by transcranial magnetic stimulation. Annals of Neurology 2003;53:263–6. https://doi.org/10.1002/ana.10468.

Plewnia C, Vonthein R, Wasserka B, Arfeller C, Naumann A, Schraven SP, et al. Treatment of chronic tinnitus with theta burst stimulation: a randomized controlled trial. Neurology 2012;78:1628–34. https://doi.org/10.1212/WNL.0b013e3182574ef9.

Polanía R, Nitsche MA, Ruff CC. Studying and modifying brain function with non-invasive brain stimulation. Nature Neuroscience 2018;21:174–87. https://doi.org/10.1038/s41593-017-0054-4.

Qiu S, Wang S, Yi W, Zhang C, He H. The lasting effects of 1Hz repetitive transcranial magnetic stimulation on resting state EEG in healthy subjects. Annu Int Conf IEEE Eng Med Biol Soc 2019;2019:5918–22. https://doi.org/10.1109/EMBC.2019.8857184.

Rachid F. Maintenance repetitive transcranial magnetic stimulation (rTMS) for relapse prevention in with depression: A review. Psychiatry Res 2018;262:363–72. https://doi.org/10.1016/j.psychres.2017.09.009.

Ramakers GGJ, van Zon A, Stegeman I, Grolman W. The effect of cochlear implantation on tinnitus in patients with bilateral hearing loss: A systematic review. Laryngoscope 2015;125:2584–92. https://doi.org/10.1002/lary.25370.

Reavis KM, Chang JE, Zeng F-G. Patterned sound therapy for the treatment of tinnitus: The Hearing Journal 2010;63:21–2. https://doi.org/10.1097/01.HJ.0000390817.79500.ed.

Reavis KM, Rothholtz VS, Tang Q, Carroll JA, Djalilian H, Zeng F-G. Temporary Suppression of Tinnitus by Modulated Sounds. J Assoc Res Otolaryngol 2012;13:561–71. https://doi.org/10.1007/s10162-012-0331-6.

Riha C, Güntensperger D, Kleinjung T, Meyer M. Accounting for Heterogeneity: Mixed-Effects Models in Resting-State EEG Data in a Sample of Tinnitus Sufferers. Brain Topogr 2020. https://doi.org/10.1007/s10548-020-00772-7.

Roberts LE. Residual inhibition. Progress in Brain Research, vol. 166, Elsevier; 2007, p. 487–95. https://doi.org/10.1016/S0079-6123(07)66047-6.

Roberts LE, Eggermont JJ, Caspary DM, Shore SE, Melcher JR, Kaltenbach JA. Ringing Ears: The Neuroscience of Tinnitus. Journal of Neuroscience 2010;30:14972–9. https://doi.org/10.1523/JNEUROSCI.4028-10.2010.

Roberts LE, Moffat G, Baumann M, Ward LM, Bosnyak DJ. Residual Inhibition Functions Overlap Tinnitus Spectra and the Region of Auditory Threshold Shift. Journal of the Association for Research in Otolaryngology 2008;9:417–35. https://doi.org/10.1007/s10162-008-0136-9.

Roberts LE, Moffat G, Bosnyak DJ. Residual inhibition functions in relation to tinnitus spectra and auditory threshold shift. Acta Oto-Laryngologica 2006;126:27–33. https://doi.org/10.1080/03655230600895358.

Rosing SN, Schmidt JH, Wedderkopp N, Baguley DM. Prevalence of tinnitus and hyperacusis in children and adolescents: a systematic review. BMJ Open 2016;6:e010596. https://doi.org/10.1136/bmjopen-2015-010596.

Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. Clin Neurophysiol 2015;126:1071–107. https://doi.org/10.1016/j.clinph.2015.02.001.

Roth Y, Amir A, Levkovitz Y, Zangen A. Three-Dimensional Distribution of the Electric Field Induced in the Brain by Transcranial Magnetic Stimulation Using Figure-8 and Deep H-Coils. Journal of Clinical Neurophysiology 2007;24:31–8. https://doi.org/10.1097/WNP.0b013e31802fa393.

Saari J, Kallioniemi E, Tarvainen M, Julkunen P. Oscillatory TMS-EEG-Responses as a Measure of the Cortical Excitability Threshold. IEEE Trans Neural Syst Rehabil Eng 2018;26:383–91. https://doi.org/10.1109/TNSRE.2017.2779135.

Sahlsten H, Holm A, Rauhala E, Takala M, Löyttyniemi E, Karukivi M, et al. Neuronavigated Versus Non-navigated Repetitive Transcranial Magnetic Stimulation for Chronic Tinnitus: A Randomized Study. Trends in Hearing 2019;23:233121651882219. https://doi.org/10.1177/2331216518822198.

Sahlsten H, Isohanni J, Haapaniemi J, Salonen J, Paavola J, Loyttyniemi E, et al. Electric field navigated transcranial magnetic stimulation for chronic tinnitus: A pilot study. Int J Audiol 2015;54:899–909. https://doi.org/10.3109/14992027.2015.1054041.

Sahlsten H, Virtanen J, Joutsa J, Niinivirta-Joutsa K, Loyttyniemi E, Johansson R, et al. Electric field-navigated transcranial magnetic stimulation for chronic tinnitus: a randomized, placebo-controlled study. Int J Audiol 2017;56:692–700. https://doi.org/10.1080/14992027.2017.1313461.

Salazar JW, Meisel K, Smith ER, Quiggle A, McCoy DB, Amans MR. Depression in Patients with Tinnitus: A Systematic Review. Otolaryngol Head Neck Surg 2019;161:28–35. https://doi.org/10.1177/0194599819835178.

Sanders PJ, Doborjeh ZG, Doborjeh MG, Kasabov NK, Searchfield GD. Prediction of Acoustic Residual Inhibition of Tinnitus Using a Brain-Inspired Spiking Neural Network Model. Brain Sciences 2021;11:52. https://doi.org/10.3390/brainsci11010052.

Schaette R, König O, Hornig D, Gross M, Kempter R. Acoustic stimulation treatments against tinnitus could be most effective when tinnitus pitch is within the stimulated frequency range. Hearing Research 2010;269:95–101. https://doi.org/10.1016/j.heares.2010.06.022.

Schaette R, McAlpine D. Tinnitus with a normal audiogram: physiological evidence for hidden hearing loss and computational model. J Neurosci 2011;31:13452–7. https://doi.org/10.1523/JNEUROSCI.2156-11.2011.

Schaette R, Turtle C, Munro KJ. Reversible Induction of Phantom Auditory Sensations through Simulated Unilateral Hearing Loss. PLoS One 2012;7. https://doi.org/10.1371/journal.pone.0035238.

Schecklmann M, Giani A, Tupak S, Langguth B, Raab V, Polak T, et al. Neuronavigated left temporal continuous theta burst stimulation in chronic tinnitus. Restor Neurol Neurosci 2016;34:165–75. https://doi.org/10.3233/RNN-150518.

Schecklmann M, Landgrebe M, Kleinjung T, Frank E, Sand PG, Rupprecht R, et al. Changes in motor cortex excitability associated with temporal repetitive transcranial magnetic stimulation in tinnitus: hints for cross-modal plasticity? BMC Neurosci 2014a;15:71. https://doi.org/10.1186/1471-2202-15-71.

Schecklmann M, Landgrebe M, Langguth B, TRI Database Study Group. Phenotypic characteristics of hyperacusis in tinnitus. PLoS ONE 2014b;9:e86944. https://doi.org/10.1371/journal.pone.0086944.

Schecklmann M, Landgrebe M, Poeppl TB, Kreuzer P, Männer P, Marienhagen J, et al. Neural correlates of tinnitus duration and Distress: A positron emission tomography study. Human Brain Mapping 2013a;34:233–40. https://doi.org/10.1002/hbm.21426.

Schecklmann M, Lehner A, Gollmitzer J, Schmidt E, Schlee W, Langguth B. Repetitive transcranial magnetic stimulation induces oscillatory power changes in chronic tinnitus. Frontiers in Cellular Neuroscience 2015;9. https://doi.org/10.3389/fncel.2015.00421.

Schecklmann M, Lehner A, Poeppl TB, Kreuzer PM, Rupprecht R, Rackl J, et al. Auditory cortex is implicated in tinnitus distress: a voxel-based morphometry study. Brain Struct Funct 2013b;218:1061–70. https://doi.org/10.1007/s00429-013-0520-z.

Schecklmann M, Vielsmeier V, Steffens T, Landgrebe M, Langguth B, Kleinjung T. Relationship between Audiometric Slope and Tinnitus Pitch in Tinnitus Patients: Insights into the Mechanisms of Tinnitus Generation. PLoS One 2012;7. https://doi.org/10.1371/journal.pone.0034878.

Schlee W, Hall DA, Canlon B, Cima RFF, de Kleine E, Hauck F, et al. Innovations in Doctoral Training and Research on Tinnitus: The European School on Interdisciplinary Tinnitus Research (ESIT) Perspective. Front Aging Neurosci 2018;9. https://doi.org/10.3389/fnagi.2017.00447.

Schlee W, Hartmann T, Langguth B, Weisz N. Abnormal resting-state cortical coupling in chronic tinnitus. BMC Neuroscience 2009a;10:11. https://doi.org/10.1186/1471-2202-10-11.

Schlee W, Mueller N, Hartmann T, Keil J, Lorenz I, Weisz N. Mapping cortical hubs in tinnitus. BMC Biol 2009b;7:80. https://doi.org/10.1186/1741-7007-7-80.

Schlee W, Schecklmann M, Lehner A, Kreuzer PM, Vielsmeier V, Poeppl TB, et al. Reduced Variability of Auditory Alpha Activity in Chronic Tinnitus. Neural Plasticity 2014;2014:1–9. https://doi.org/10.1155/2014/436146.

Schoisswohl S, Agrawal K, Simoes J, Neff P, Schlee W, Langguth B, et al. RTMS parameters in tinnitus trials: a systematic review. Sci Rep 2019a;9:1–11. https://doi.org/10.1038/s41598-019-48750-9.

Schoisswohl S, Arnds J, Schecklmann M, Langguth B, Schlee W, Neff P. Amplitude Modulated Noise for Tinnitus Suppression in Tonal and Noise-Like Tinnitus. AUD 2019b;24:309–21. https://doi.org/10.1159/000504593.

Schoisswohl S, Langguth B, Hebel T, Abdelnaim M, Volberg G, Schecklmann M. Towards personalized rTMS in tinnitus: reliability of individualized stimulation protocols in behavioral and electrophysiological responses. MedRxiv 2021:2021.01.11.21249600. https://doi.org/10.1101/2021.01.11.21249600.

Schoisswohl S, Langguth B, Schecklmann M. Short-Term Tinnitus Suppression With Electric-Field Guided rTMS for Individualizing rTMS Treatment: A Technical Feasibility Report. Front Neurol 2020a;11:86. https://doi.org/10.3389/fneur.2020.00086.

Schoisswohl S, Schecklmann M, Langguth B, Schlee W, Neff P. Neurophysiological correlates of residual inhibition in tinnitus: Hints for trait-like EEG power spectra. BioRxiv 2020b:2020.12.15.422892. https://doi.org/10.1101/2020.12.15.422892.

Searchfield GD, Durai M, Linford T. A State-of-the-Art Review: Personalization of Tinnitus Sound Therapy. Frontiers in Psychology 2017;8. https://doi.org/10.3389/fpsyg.2017.01599.

Sedley W, Gander PE, Kumar S, Oya H, Kovach CK, Nourski KV, et al. Intracranial Mapping of a Cortical Tinnitus System using Residual Inhibition. Current Biology 2015;25:1208–14. https://doi.org/10.1016/j.cub.2015.02.075.

Sedley W, Teki S, Kumar S, Barnes GR, Bamiou D-E, Griffiths TD. Single-subject oscillatory gamma responses in tinnitus. Brain 2012;135:3089–100. https://doi.org/10.1093/brain/aws220.

Sereda M, Xia J, El Refaie A, Hall DA, Hoare DJ. Sound therapy (using amplification devices and/or sound generators) for tinnitus. Cochrane Database Syst Rev 2018;12:CD013094. https://doi.org/10.1002/14651858.CD013094.pub2.

Shargorodsky J, Curhan GC, Farwell WR. Prevalence and characteristics of tinnitus among US adults. Am J Med 2010;123:711–8. https://doi.org/10.1016/j.amjmed.2010.02.015.

Shekhawat GS, Kobayashi K, Searchfield GD. Methodology for studying the transient effects of transcranial direct current stimulation combined with auditory residual inhibition on tinnitus. Journal of Neuroscience Methods 2015;239:28–33. https://doi.org/10.1016/j.jneumeth.2014.09.025.

Shore SE, Roberts LE, Langguth B. Maladaptive plasticity in tinnitus-triggers, mechanisms and treatment. Nat Rev Neurol 2016;12:150–60. https://doi.org/10.1038/nrneurol.2016.12.

Shoushtarian M, Alizadehsani R, Khosravi A, Acevedo N, McKay CM, Nahavandi S, et al. Objective measurement of tinnitus using functional near-infrared spectroscopy and machine learning. PLOS ONE 2020;15:e0241695. https://doi.org/10.1371/journal.pone.0241695.

Siebner HR, Hartwigsen G, Kassuba T, Rothwell JC. How does transcranial magnetic stimulation modify neuronal activity in the brain? Implications for studies of cognition. Cortex 2009;45:1035–42. https://doi.org/10.1016/j.cortex.2009.02.007.

Siebner HR, Lang N, Rizzo V, Nitsche MA, Paulus W, Lemon RN, et al. Preconditioning of low-frequency repetitive transcranial magnetic stimulation with transcranial direct current stimulation: evidence for homeostatic plasticity in the human motor cortex. J Neurosci 2004;24:3379–85. https://doi.org/10.1523/JNEUROSCI.5316-03.2004.

Siebner HR, Rothwell J. Transcranial magnetic stimulation: new insights into representational cortical plasticity. Exp Brain Res 2003;148:1–16. https://doi.org/10.1007/s00221-002-1234-2.

Silvanto J, Pascual-Leone A. State-Dependency of Transcranial Magnetic Stimulation. Brain Topogr 2008;21:1–10. https://doi.org/10.1007/s10548-008-0067-0.

Simoes J, Neff P, Schoisswohl S, Bulla J, Schecklmann M, Harrison S, et al. Toward Personalized Tinnitus Treatment: An Exploratory Study Based on Internet Crowdsensing. Front Public Health 2019;7:157. https://doi.org/10.3389/fpubh.2019.00157.

Sockalingam R, Dunphy L, Nam K-E, Gulliver M. Effectiveness of frequency-matched masking and residual inhibition in tinnitus therapy: A preliminary study. Audiological Medicine 2007;5:92–102. https://doi.org/10.1080/16513860701362124.

Soleimani R, Jalali MM, Hasandokht T. Therapeutic impact of repetitive transcranial magnetic stimulation (rTMS) on tinnitus: a systematic review and meta-analysis. European Archives of Oto-Rhino-Laryngology 2016;273:1663–75. https://doi.org/10.1007/s00405-015-3642-5.

Sommer M, Wu T, Tergau F, Paulus W. Intra- and interindividual variability of motor responses to repetitive transcranial magnetic stimulation. Clinical Neurophysiology 2002;113:265–9. https://doi.org/10.1016/S1388-2457(01)00726-X.

Stein A, Engell A, Lau P, Wunderlich R, Junghoefer M, Wollbrink A, et al. Enhancing inhibition-induced plasticity in tinnitus--spectral energy contrasts in tailor-made notched music matter. PLoS ONE 2015;10:e0126494. https://doi.org/10.1371/journal.pone.0126494.

Tass PA, Adamchic I, Freund H-J, von Stackelberg T, Hauptmann C. Counteracting tinnitus by acoustic coordinated reset neuromodulation. Restor Neurol Neurosci 2012;30:137–59. https://doi.org/10.3233/RNN-2012-110218.

Tass PA, Popovych OV. Unlearning tinnitus-related cerebral synchrony with acoustic coordinated reset stimulation: theoretical concept and modelling. Biol Cybern 2012;106:27–36. https://doi.org/10.1007/s00422-012-0479-5.

Teismann H, Wollbrink A, Okamoto H, Schlaug G, Rudack C, Pantev C. Combining Transcranial Direct Current Stimulation and Tailor-Made Notched Music Training to Decrease Tinnitus-Related Distress – A Pilot Study. PLOS ONE 2014;9:e89904. https://doi.org/10.1371/journal.pone.0089904.

Terranova C, Rizzo V, Cacciola A, Chillemi G, Calamuneri A, Milardi D, et al. Is There a Future for Non-invasive Brain Stimulation as a Therapeutic Tool? Front Neurol 2019;9:1146. https://doi.org/10.3389/fneur.2018.01146.

Terry AMP, Jones DM, Davis BR, Slater R. Parametric Studies of Tinnitus Masking and Residual Inhibition. British Journal of Audiology 1983;17:245–56. https://doi.org/10.3109/03005368309081485.

Thabit MN, Fouad N, Shahat B, Youssif M. Combined Central and Peripheral Stimulation for Treatment of Chronic Tinnitus: A Randomized Pilot Study. Neurorehabilitation and Neural Repair 2015;29:224–33. https://doi.org/10.1177/1545968314542616.

Theodoroff SM, Folmer RL. Repetitive Transcranial Magnetic Stimulation as a Treatment for Chronic Tinnitus: A Critical Review 2013;34:10.

Theodoroff SM, Schuette A, Griest S, Henry JA. Individual Patient Factors Associated with Effective Tinnitus Treatment. J Am Acad Audiol 2014;25:631–43. https://doi.org/10.3766/jaaa.25.7.2.

Thut G, Pascual-Leone A. A Review of Combined TMS-EEG Studies to Characterize Lasting Effects of Repetitive TMS and Assess Their Usefulness in Cognitive and Clinical Neuroscience. Brain Topography 2010;22:219–32. https://doi.org/10.1007/s10548-009-0115-4.

Thut G, Veniero D, Romei V, Miniussi C, Schyns P, Gross J. Rhythmic TMS Causes Local Entrainment of Natural Oscillatory Signatures. Current Biology 2011;21:1176–85. https://doi.org/10.1016/j.cub.2011.05.049.

Tremblay S, Rogasch NC, Premoli I, Blumberger DM, Casarotto S, Chen R, et al. Clinical utility and prospective of TMS–EEG. Clinical Neurophysiology 2019;130:802–44. https://doi.org/10.1016/j.clinph.2019.01.001.

Trevis KJ, McLachlan NM, Wilson SJ. Psychological mediators of chronic tinnitus: The critical role of depression. J Affect Disord 2016;204:234–40. https://doi.org/10.1016/j.jad.2016.06.055.

Tunkel DE, Bauer CA, Sun GH, Rosenfeld RM, Chandrasekhar SS, Eugene R. Cunningham J, et al. Clinical Practice Guideline: Tinnitus. Otolaryngology–Head and Neck Surgery 2014. https://doi.org/10.1177/0194599814545325.

Tyler R, Stocking C, Secor C, Slattery WH. Amplitude Modulated S-Tones Can Be Superior to Noise for Tinnitus Reduction. American Journal of Audiology 2014;23:303. https://doi.org/10.1044/2014_AJA-14-0009.

Tyler RS, Oleson J, Noble W, Coelho C, Ji H. Clinical trials for tinnitus: study populations, designs, measurement variables, and data analysis. In: Langguth B, Hajak G, Kleinjung T, Cacace A, Møller AR, editors. Progress in Brain Research, vol. 166, Elsevier; 2007, p. 499–509. https://doi.org/10.1016/S0079-6123(07)66048-8.

Van der Wal A, Luyten T, Cardon E, Jacquemin L, Vanderveken OM, Topsakal V, et al. Sex Differences in the Response to Different Tinnitus Treatment. Front Neurosci 2020;14:422. https://doi.org/10.3389/fnins.2020.00422.

Van Doren J, Langguth B, Schecklmann M. TMS-related potentials and artifacts in combined TMS-EEG measurements: Comparison of three different TMS devices. Neurophysiol Clin 2015;45:159–66. https://doi.org/10.1016/j.neucli.2015.02.002.

Vanneste S, De Ridder D. Differences between a single session and repeated sessions of 1 Hz TMS by double-cone coil prefrontal stimulation for the improvement of tinnitus. Brain Stimul 2013;6:155–9. https://doi.org/10.1016/j.brs.2012.03.019.

Vanneste S, De Ridder D. The auditory and non-auditory brain areas involved in tinnitus. An emergent property of multiple parallel overlapping subnetworks. Front Syst Neurosci 2012;6:31. https://doi.org/10.3389/fnsys.2012.00031.

Vanneste Sven, van de Heyning P, De Ridder D. The neural network of phantom sound changes over time: a comparison between recent-onset and chronic tinnitus patients. Eur J Neurosci 2011a;34:718–31. https://doi.org/10.1111/j.1460-9568.2011.07793.x.

Vanneste S., Heyning PV de, Ridder DD. Contralateral parahippocampal gamma-band activity determines noise-like tinnitus laterality: a region of interest analysis. Neuroscience 2011c;199:481–90. https://doi.org/10.1016/j.neuroscience.2011.07.067.

Vanneste S, Heyning PVD, Ridder DD. Tinnitus: A Large VBM-EEG Correlational Study. PLOS ONE 2015;10:e0115122. https://doi.org/10.1371/journal.pone.0115122.

Vanneste Sven, Plazier M, Van de Heyning P, De Ridder D. Repetitive transcranial magnetic stimulation frequency dependent tinnitus improvement by double cone coil prefrontal stimulation. J Neurol Neurosurg Psychiatry 2011b;82:1160–4. https://doi.org/10.1136/jnnp.2010.213959.

Vernon J, Fenwick J. Identification of Tinnitus: A Plea for Standardization. The Journal of Laryngology & Otology 1984;98:45–53. https://doi.org/10.1017/S1755146300090107.

Vernon JA, Meikle MB. Tinnitus: clinical measurement. Otolaryngologic Clinics of North America 2003;36:293–305. https://doi.org/10.1016/S0030-6665(02)00162-7.

Vielsmeier V, Schecklmann M, Schlee W, Kreuzer PM, Poeppl TB, Rupprecht R, et al. A Pilot Study of Peripheral Muscle Magnetic Stimulation as Add-on Treatment to Repetitive Transcranial Magnetic Stimulation in Chronic Tinnitus. Front Neurosci 2018;12:68. https://doi.org/10.3389/fnins.2018.00068.

Wagner J, Makeig S, Hoopes D, Gola M. Can Oscillatory Alpha-Gamma Phase-Amplitude Coupling be Used to Understand and Enhance TMS Effects? Front Hum Neurosci 2019;13. https://doi.org/10.3389/fnhum.2019.00263.

Wang H, Tang D, Wu Y, Zhou L, Sun S. The state of the art of sound therapy for subjective tinnitus in adults. Therapeutic Advances in Chronic Disease 2020;11:2040622320956426. https://doi.org/10.1177/2040622320956426.

Wegger M, Ovesen T, Larsen DG. Acoustic Coordinated Reset Neuromodulation: A Systematic Review of a Novel Therapy for Tinnitus. Front Neurol 2017;8. https://doi.org/10.3389/fneur.2017.00036.

Weidt S, Delsignore A, Meyer M, Rufer M, Peter N, Drabe N, et al. Which tinnitus-related characteristics affect current health-related quality of life and depression? A cross-sectional cohort study. Psychiatry Res 2016;237:114–21. https://doi.org/10.1016/j.psychres.2016.01.065.

Weisz N, Dohrmann K, Elbert T. The relevance of spontaneous activity for the coding of the tinnitus sensation. Progress in Brain Research, vol. 166, Elsevier; 2007a, p. 61–70. https://doi.org/10.1016/S0079-6123(07)66006-3.

Weisz N, Hartmann T, Dohrmann K, Schlee W, Norena A. High-frequency tinnitus without hearing loss does not mean absence of deafferentation. Hear Res 2006;222:108–14. https://doi.org/10.1016/j.heares.2006.09.003.

Weisz N, Hartmann T, Müller N, Lorenz I, Obleser J. Alpha Rhythms in Audition: Cognitive and Clinical Perspectives. Frontiers in Psychology 2011;2. https://doi.org/10.3389/fpsyg.2011.00073.

Weisz N, Lüchinger C, Thut G, Müller N. Effects of individual alpha rTMS applied to the auditory cortex and its implications for the treatment of chronic tinnitus. Human Brain Mapping 2014;35:14–29. https://doi.org/10.1002/hbm.22152.

Weisz N, Moratti S, Meinzer M, Dohrmann K, Elbert T. Tinnitus Perception and Distress Is Related to Abnormal Spontaneous Brain Activity as Measured by Magnetoencephalography. PLoS Medicine 2005;2:e153. https://doi.org/10.1371/journal.pmed.0020153.

Weisz N, Müller S, Schlee W, Dohrmann K, Hartmann T, Elbert T. The neural code of auditory phantom perception. J Neurosci 2007b;27:1479–84. https://doi.org/10.1523/JNEUROSCI.3711-06.2007.

Weisz N, Steidle L, Lorenz I. Formerly known as inhibitory: effects of 1-Hz rTMS on auditory cortex are state-dependent: Formerly known as inhibitory. European Journal of Neuroscience 2012;36:2077–87. https://doi.org/10.1111/j.1460-9568.2012.08097.x.

Woźniak-Kwaśniewska A, Szekely D, Aussedat P, Bougerol T, David O. Changes of oscillatory brain activity induced by repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in healthy subjects. NeuroImage 2014;88:91–9. https://doi.org/10.1016/j.neuroimage.2013.11.029.

Wunderlich R, Lau P, Stein A, Engell A, Wollbrink A, Rudack C, et al. Impact of Spectral Notch Width on Neurophysiological Plasticity and Clinical Effectiveness of the Tailor-Made Notched Music Training. PLOS ONE 2015;10:e0138595. https://doi.org/10.1371/journal.pone.0138595.

Yang S, Weiner BD, Zhang LS, Cho S-J, Bao S. Homeostatic plasticity drives tinnitus perception in an animal model. Proc Natl Acad Sci USA 2011;108:14974–9. https://doi.org/10.1073/pnas.1107998108.

Zaehle T, Beretta M, Jäncke L, Herrmann CS, Sandmann P. Excitability changes induced in the human auditory cortex by transcranial direct current stimulation: direct electrophysiological evidence. Exp Brain Res 2011;215:135–40. https://doi.org/10.1007/s00221-011-2879-5.

Zenner H-P, Delb W, Kröner-Herwig B, Jäger B, Peroz I, Hesse G, et al. A multidisciplinary systematic review of the treatment for chronic idiopathic tinnitus. European Archives of Oto-Rhino-Laryngology 2017;274:2079–91. https://doi.org/10.1007/s00405-016-4401-y.

Zenner HP, Maddalena HD, Zalaman IM. Validity and reliability study of three tinnitus self-assessment scales: loudness, annoyance and change. Acta Oto-Laryngologica 2005;125:1184–8. https://doi.org/10.1080/00016480510012282.

Zobay O, Palmer AR, Hall DA, Sereda M, Adjamian P. Source Space Estimation of Oscillatory Power and Brain Connectivity in Tinnitus. PLOS ONE 2015;10:e0120123. https://doi.org/10.1371/journal.pone.0120123.

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11.1. Supplemental material – study 1

11.1.1. Tables

Table S1

Tinnitus loudness per condition.

	Total				T0			
	M ± SD	**Md**	**Min**	**Max**	**M ± SD**	**Md**	**Min**	**Max**
IBP	87.24 ± 23.93	100.00	.00	120.00	77.59 ± 36.22	100.00	.00	120.l00
IPB10	88.77 ± 20.82	100.00	10.00	140.00	77.95 ± 32.56	80.00	10.00	140.00
IBP10_MML	91.63 ± 19.01	100.00	10.00	110.00	81.72 ± 28.17	100.00	10.00	110.00
IBP40	86.16 ± 24.60	100.00	.00	130.00	77.59 ± 37.57	100.00	.00	130.00
WN	90.00 ± 23.29	100.00	.00	140.00	77.59 ± 37.00	100.00	.00	140.00
WN10	89.41 ± 20.93	100.00	.00	120.00	77.24 ± 32.28	80.00	.00	120.00
WN40	87.95 ± 26.51	100.00	.00	130.00	73.10 ± 41.76	100.00	.00	130.00
Noise-like								
IBP	78.98 ± 27.86	90.00	.00	120.00	61.43 ± 38.00	65.00	.00	120.00
IPB10	80.71 ± 24.67	90.00	10.00	120.00	62.86 ± 34.96	50.00	10.00	120.00
IBP10_MML	85.92 ± 24.49	100.00	10.00	110.00	69.29 ± 33.16	80.00	10.00	110.00
IBP40	80.10 ± 26.81	90.00	.00	120.00	62.86 ± 37.50	55.00	.00	120.00
WN	84.49 ± 26.56	100.00	.00	110.00	63.57 ± 37.54	70.00	.00	110.00
WN10	84.18 ± 24.41	100.00	.00	120.00	64.29 ± 36.94	65.00	.00	120.00
WN40	80.61 ± 31.29	100.00	.00	120.00	63.57 ± 44.13	70.00	.00	120.00
Tonal								
IBP	94.95 ± 16.24	100.00	10.00	120.00	92.67 ± 27.89	100.00	10.00	120.00
IPB10	96.29 ± 12.50	100.00	50.00	140.00	92.00 ± 23.36	100.00	50.00	140.00
IBP10_MML	96.95 ± 9.11	100.00	50.00	110.00	93.33 ± 16.33	100.00	50.00	110.00
IBP40	91.81 ± 20.93	100.00	10.00	130.00	91.33 ± 33.14	100.00	10.00	130.00
WN	95.14 ± 18.46	100.00	.00	140.00	90.67 ± 32.40	100.00	.00	140.00
WN10	94.29 ± 15.68	100.00	40.00	120.00	89.33 ± 22.19	100.00	40.00	120.00
WN40	94.10 ± 19.05	100.00	.00	130.00	82.00 ± 38.77	100.00	.00	130.00

M = mean; SD = standard deviation; Md = median; Min = minimum; Max = maximum; T0 = immediately after stimulation offset.

Table S2

Model fitting.

	$R^2_{(marginal)}$	$R^2_{(conditional)}$	df	AIC	BIC	logLik	LRT	p
Intercept only: response ~ 1 + 1|id)	.00	.51	3	12046.00	12061.00	-6019.00		
Fitted model: response ~ condition + time*group + 1|id)	.17	.60	22	11774.00	11890.00	-5865.20	309.22	<.01

DF = degrees of freedom; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; logLik = log-likelihood; LRT = Likelihood Ratio Test.

Table S3.

Stimulus evaluation.

	Arousal				Valence			
	M ± SD	**Md**	**Min**	**Max**	**M ± SD**	**Md**	**Min**	**Max**
IBP	87.24 ± 23.93	100.00	.00	120.00	77.59 ± 36.22	100.00	.00	120.00
IPB10	88.77 ± 20.82	100.00	10.00	140.00	77.95 ± 32.56	80.00	10.00	140.00
IBP10_MML	91.63 ± 19.01	100.00	10.00	110.00	81.72 ± 28.17	100.00	10.00	110.00
IBP40	86.16 ± 24.60	100.00	.00	130.00	77.59 ± 37.57	100.00	.00	130.00
WN	90.00 ± 23.29	100.00	.00	140.00	77.59 ± 37.00	100.00	.00	140.00
WN10	89.41 ± 20.93	100.00	.00	120.00	77.24 ± 32.28	80.00	.00	120.00
WN40	87.95 ± 26.51	100.00	.00	130.00	73.10 ± 41.76	100.00	.00	130.00
Noise-like								
IBP	78.98 ± 27.86	90.00	.00	120.00	61.43 ± 38.00	65.00	.00	120.00
IPB10	80.71 ± 24.67	90.00	10.00	120.00	62.86 ± 34.96	50.00	10.00	120.00
IBP10_MML	85.92 ± 24.49	100.00	10.00	110.00	69.29 ± 33.16	80.00	10.00	110.00
IBP40	80.10 ± 26.81	90.00	.00	120.00	62.86 ± 37.50	55.00	.00	120.00
WN	84.49 ± 26.56	100.00	.00	110.00	63.57 ± 37.54	70.00	.00	110.00
WN10	84.18 ± 24.41	100.00	.00	120.00	64.29 ± 36.94	65.00	.00	120.00
WN40	80.61 ± 31.29	100.00	.00	120.00	63.57 ± 44.13	70.00	.00	120.00
Tonal								
IBP	94.95 ± 16.24	100.00	10.00	120.00	92.67 ± 27.89	100.00	10.00	120.00
IPB10	96.29 ± 12.50	100.00	50.00	140.00	92.00 ± 23.36	100.00	50.00	140.00
IBP10_MML	96.95 ± 9.11	100.00	50.00	110.00	93.33 ± 16.33	100.00	50.00	110.00
IBP40	91.81 ± 20.93	100.00	10.00	130.00	91.33 ± 33.14	100.00	10.00	130.00
WN	95.14 ± 18.46	100.00	.00	140.00	90.67 ± 32.40	100.00	.00	140.00
WN10	94.29 ± 15.68	100.00	40.00	120.00	89.33 ± 22.19	100.00	40.00	120.00
WN40	94.10 ± 19.05	100.00	.00	130.00	82.00 ± 38.77	100.00	.00	130.00

M = mean; SD = minimum; Max = maximum.

Table S4.

Model fitting - arousal and valence.

Model	$R^2_{(marginal)}$	$R^2_{(conditional)}$	df	AIC	BIC	logLik	LRT	p
Arousal								
Intercept only: response ~ 1 + 1|id)	.00	.33	3	776.28	786.22	-385.14		
Fitted model: response ~ condition + 1|id)	.09	.42	9	759.72	789.54	-370.86	28.56	< .01
Valence								
Intercept only: response ~ 1 + 1|id)	.00	.37	3	858.16	868.10	-426.08		
Fitted model: response ~ condition + 1|id)	.06	.42	9	851.69	881.51	-416.84	18.84	< .01

Df = degrees of freedom; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; logLik = log-likelihood; LRT = Likelihood Ratio Test.

11.1.2. Figures

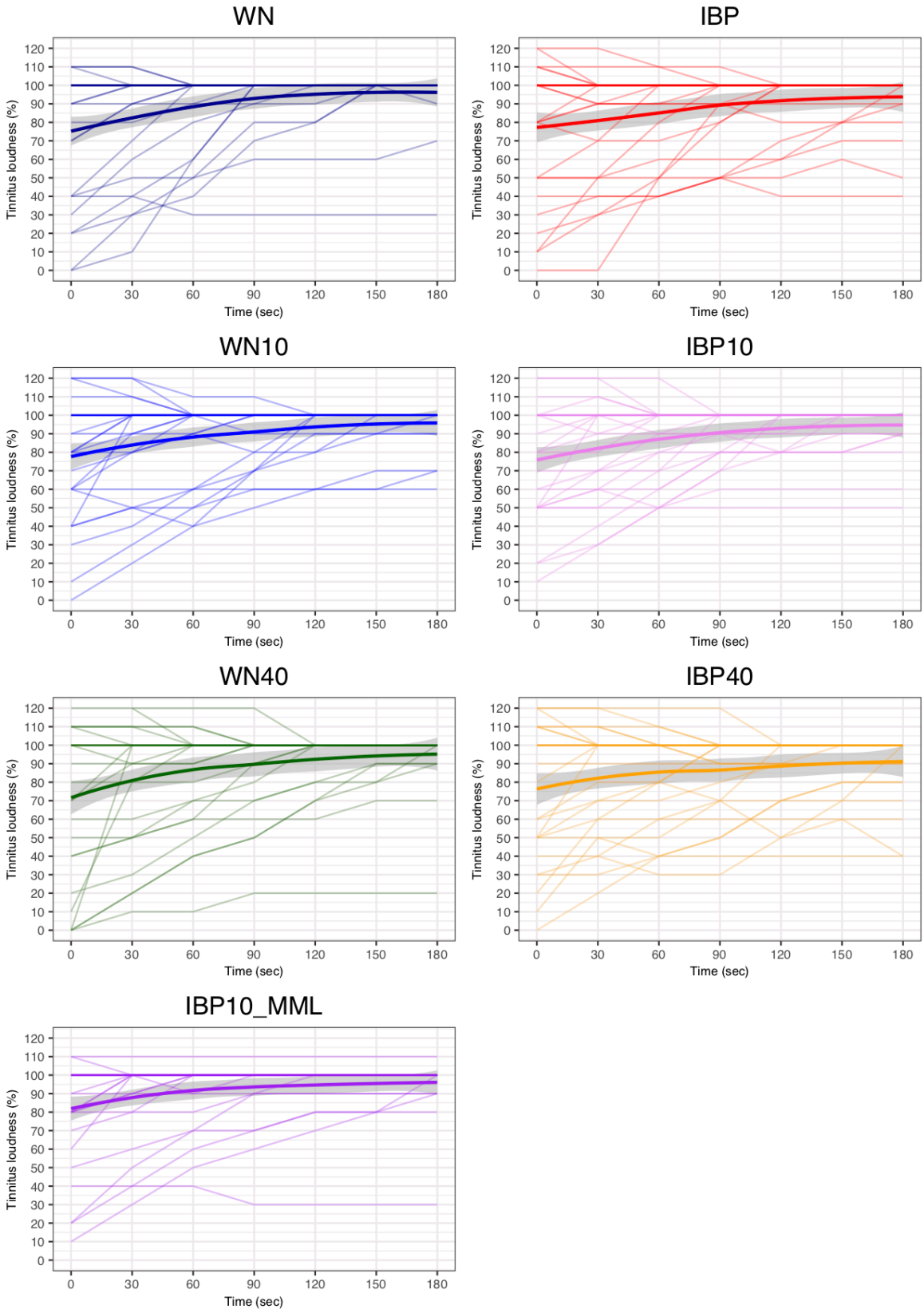

Figure S1. **Tinnitus loudness time curve - single participant response.**
Tinnitus loudness ratings are illustrated on a single participant level for all rating timepoints separated for each stimuli. Thick lines show the mean tinnitus loudness (%) for each stimulus, standard deviations are illustrated as grey ribbons.

11.2. Supplemental material – study 2

11.2.1. Tables

Table S5.
Tinnitus loudness per condition.

	Total				T0			
	M ± SD	**Md**	**Min**	**Max**	**M ± SD**	**Md**	**Min**	**Max**
Total sample								
WN	88.29 ± 19.26	100.00	20.00	110.00	88.00 ± 21.60	90.00	20.00	110.00
IBP	87.24 ± 17.73	90.00	20.00	110.00	86.67 ± 21.95	90.00	20.00	110.00
IBS	92.60 ± 14.77	100.00	50.00	110.00	93.11 ± 16.35	100.00	50.00	110.00

WN = white noise; IBP = individualized bandpass filtered white noise; IBS = individualized bandstop filtered white noise; M = mean; SD = standard deviation; Md = median; Min = minimum; Max = maximum; T0 = immediately after stimulation offset.

Table S6.
Model fitting - tinnitus loudness ratings.

	$R^2_{(marginal)}$	$R^2_{(conditional)}$	df	AIC	BIC	logLik	LRT	p
Total sample								
Intercept only: response~1 + 1|id)	0	.59	3	7402.10	7416.70	-3698.10		
Fitted model: response ~ condition + 1|id)	.02	.61	5	7364.20	7388.50	-3677.10	41.88	<.001

DF = degrees of freedom; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; logLik = log-likelihood; LRT = Likelihood Ratio Test.

Table S7.
Fixed effect testing - tinnitus loudness ratings.

	numDF	denDF	F	p
Condition	2.00	900.00	21.43	< .001

numDF = degrees of freedom numerator; denDF = degrees of freedom denominator.

Table S8.

Stimulus evaluation.

	Valence				Arousal			
	M ± SD	**Md**	**Min**	**Max**	**M ± SD**	**Md**	**Min**	**Max**
WN	.18 ± 1.83	0	-4.00	4.00	-.16 ± 1.68	0	-4.00	3.00
IBP	-.40 ± 2.18	0	-4.00	4.00	.51 ± 1.73	0	-3.00	3.00
IBS	1.02 ± 2.09	2.00	-4.00	4.00	-.84 ± 1.82	0	-4.00	3.00
Male								
WN	.03 ± 1.47	0	-4.00	3.00	.19 ± 1.25	0	-3.00	3.00
IBP	-.39 ± 2.26	0	-4.00	4.00	.68 ± 1.58	0	-2.00	3.00
IBS	.87 ± 1.98	1.00	-4.00	4.00	-.52 ± 1.69	0	-4.00	3.00
Female								
WN	.50 ± 2.47	0	-4.00	4.00	.50 ± 2.47	0	-4.00	4.00
IBP	-.43 ± 2.06	0	-4.00	3.00	-.43 ± 2.06	0	-4.00	3.00
IBS	1.36 ± 2.37	2.00	-4.00	4.00	-1.57 ± 1.95	-2.00	-4.00	2.00

WN = white noise; IBP = individualized bandpass filtered white noise; IBS = individualized bandstop filtered white noise; M = mean; SD = standard deviation; Md = median; Min = minimum; Max = maximum.

Table S9.

Model fitting – valence and arousal ratings.

Model	$R^2_{(marginal)}$	$R^2_{(conditional)}$	df	AIC	BIC	logLik	LRT	p
Arousal								
Intercept only: response ~ 1 + 1|id)	0	.32	3	577.52	586.23	-285.76		
Fitted model: response ~ condition + 1|id)	.01	.43	5	564.91	579.44	-277.46	16.60	< .001
Valence								
Intercept only: response ~ 1 + 1|id)	0	.33	3	543.75	552.46	-268.87		
Fitted model: response ~ condition + gender + 1|id)	.15	.35	6	526.72	544.15	-257.36	20.03	< .001

Df = degrees of freedom; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; logLik = log-likelihood; LRT = Likelihood Ratio Test.

Table S10.
Fixed effect testing – valence and arousal ratings.

	numDF	denDF	F	p
Arousal				
Condition	2.00	90.00	9.12	< .001
Valence				
Condition	2.00	90.00	9.76	< .001
Gender	1.00	45.00	5.70	.021

numDF = degrees of freedom numerator; denDF = degrees of freedom denominator.

Table S11.
Post-hoc Tukey contrasts for condition – stimulus evaluation.

	Valence				Arousal			
Contrast	**Estimate**	**t**	**p**	**d**	**Estimate**	**t**	**p**	**d**
WN – IBP	.58	1.71	.209	.288	-.76	-2.15	.086	.392
WN – IBS	**-.84**	**-2.49**	**.038**	**.428**	.69	2.22	.073	.388
IBP – IBS	**-1.42**	**-4.20**	**< .001**	**.665**	**1.36**	**4.37**	**< .001**	**.760**
Male – Female					**.90**	**2.33**	**.024**	**.728**

WN = white noise; IBP = individualized bandpass filtered white noise; IBS = individualized bandstop filtered white noise. Valence: Degrees of freedom = 92.00; standard error = .34; Arousal: Degrees of freedom = 92.00; standard error = .31; Gender: Degrees of freedom = 47.10; standard error = .39.

Table S12.
Cluster electrodes – total sample analysis.

	Frequency (Hz)	Cluster electrodes
Time		
Positive cluster	1 – 7	**frontal:** F3, F4, F7, F8, Fz, F1, F2, F5, F6 **central:** Cz, Pz, FC1, FC2, CP1, CP2, C1, C2, P1, P2, CPz **temporal:** C3, C4, T7, T8, FC5, FC6, FC3, FC4, C5, C6, FT7, FT8 **parietal:** P3, P4, P7, P8, CP5, CP6, CP3, CP4, P5, P6, TP7, TP8 **occipital:** O1, O2, PO3, PO4, PO7, PO8, POz, Oz
Positive cluster	26 – 45	**frontal:** F3, F4, F8, Fz, F1, F2, F5, F6 **central:** Cz, Pz, FC1, CP1, C1, P1, P2, CPz **temporal:** FC6, FC3, FC4 **parietal:** P3 **occipital:** O1, O2, PO3, PO4, PO7, PO8, POz, Oz
Negative cluster	7 – 28	**frontal:** F3, F4, F7, F8, Fz, F1, F2, F5, F6 **central:** Cz, Pz, FC1, FC2, CP1, CP2, C1, C2, P1, P2, CPz **temporal:** C3, C4, T7, T8, FC5, FC6, FC3, FC4, C5, C6, FT7, FT8 **parietal:** P3, P4, P7, P8, CP5, CP6, CP3, CP4, P5, P6, TP7, TP8 **occipital:** PO3, PO4, PO8, POz, Oz
Condition x Time		
Positive cluster	1 – 7	**frontal:** F3, F4, F7, F8, Fz, F1, F2, F5, F6 **central:** FC1, CP1, CP2, C1, C2, P1, P2, Pz, CPz **temporal:** C3, C4, T7, T8, FC5, FC6, FC3, FC4, C5, C6, FT7, FT8 **parietal:** P3, P4, P7, P8, CP5, CP6, CP3, CP4, P5, P6, TP7, TP8 **occipital:** O1, O2, PO3, PO4, PO7, PO8, POz, Oz
Positive cluster	36 – 45	**frontal:** F3, F4, F8, Fz, F1, F2, F5, F6 **central:** Pz, FC1, CP1, CP2, C1, P1, P2, CPz **temporal:** FC5 **parietal:** P3, P4, CP3, P5, TP7 **occipital:** PO3, PO4, POz
Post-hoc – pre vs. post stimulation per stimulus		
Positive cluster		
WN	1 – 7	**frontal:** F3, F4, F7, F8, Fz, F2, F5, F6 **central:** Cz, Pz, FC1, FC2, CP1, CP2, C1, P1, P2, CPz **temporal:** C3, C4, T7, T8, FC5, FC6, FC3, FC4, C5, C6, FT7, FT8 **parietal:** P3, P4, P7, P8, CP5, CP6, CP3, CP4, P5, P6, TP7, TP8 **occipital:** O1, O2, PO3, PO4, PO7, PO8, POz, Oz
IBP	1 – 6	**frontal:** F3, F4, F7, F8, Fz, F1, F2, F5, F6 **central:** Pz, FC1, FC2, CP1, CP2, C1, P1, P2, CPz **temporal:** C3, C4, T7, T8, FC5, FC6, FC3, FC4, C5, C6, FT7, FT8 **parietal:** P3, P4, P7, P8, CP5, CP6, CP3, CP4, P5, P6, TP7, TP8 **occipital:** O1, O2, PO3, PO4, PO7, PO8, POz, Oz
IBP	32 – 45	**frontal:** F3, Fz, F1, F2, F5 **central:** Cz, Pz, CP1, CP2, P1, P2, CPz **temporal:** FT7 **parietal:** P3, P5 **occipital:** PO3, PO4, POz
IBS	1 – 6	**frontal:** F3, F4, F7, F8, Fz, F1, F2, F5, F6 **central:** Cz, Pz, FC1, FC2, CP1, C1, C2, P1, P2, CPz **temporal:** C3, C4, T7, T8, FC5, FC6, FC3, FC4, C5, C6, FT7, FT8 **parietal:** P3, P4, P7, P8, CP5, CP6, CP3, CP4, P5, P6, TP7, TP8 **occipital:** O1, O2, PO3, PO4, PO7, PO8, POz, Oz
IBS	37 – 45	**frontal:** Fz, F1 **central:** Cz, Pz, FC1, CP1, CP2, C1, P1, P2, CPz **temporal:** FC3 **parietal:** P3, P4 **occipital:** PO3, PO4, POz
Negative cluster		
WN	10 – 12	**frontal:** F3, F4, Fz, F1, F2, F5, F6 **central:** Pz, FC1, FC2, CP1, CP2, C2, P1, P2 **temporal:** C4, T7, T8, FC5, FC6, FC4, C5, C6, FT7, FT8 **parietal:** P3, P4, P7, P8, CP5, CP6, CP3, CP4, P5, P6, TP7, TP8 **occipital:** PO3, PO4, POz
WN	14 – 19	**frontal:** Fz, F1, F2 **central:** Pz, FC2, CP1, CP2, C2, P1, P2, CPz **temporal:** C4, T8, C6 **parietal:** P3, P4, P8, CP6, CP4, TP8 **occipital:** POz
IBS	11 – 19	**frontal:** Fz **central:** Cz, Pz, FC1, CP1, CP2, C1, C2, P1, P2, CPz **temporal:** C3, C4, T7, T8, FC5, C5, C6 **parietal:** P3, P4, P7, CP5, CP6, CP3, CP4, P5, TP7, TP8 **occipital:** -

WN = white noise; IBP = individualized bandpass filtered white noise; IBS = individualized bandstop filtered white noise. **Note:** Electrodes within frequency clusters grouped by brain areas.

Table S13.

Cluster electrodes – non-responder vs. responder analysis.

	Frequency (Hz)	Cluster electrodes
Group		
Positive cluster	7 – 12	**frontal:** F3, F4, F8, Fz, F1, F2, F5, F6 **central:** Pz, FC1, FC2, CP1, CP2, C1, P1, P2, CPz **temporal:** C3, C4, T8, FC5, FC6, FC3, FC4, C6, FT8 **parietal:** P3, P4, P8, CP5, CP6, CP3, CP4, P5, P6, TP7, TP8 **occipital:** O1, O2, PO3, PO4, PO7, PO8, POz, Oz
Negative cluster	22 – 45	**frontal:** Fz, F1, F2 **central:** Cz, Pz, FC1, FC2, CP1, C1, P1, CPz **temporal:** C3, C5 **parietal:** P3, P7, CP5, CP3, P5, TP7 **occipital:** PO3, PO7, POz
Time		
Negative cluster	6 – 32	**frontal:** F3, F4, F7, F8, Fz, F1, F2, F5, F6 **central:** Cz, Pz, FC1, FC2, CP1, CP2, C1, C2, P1, P2, CPz **temporal:** C3, C4, T7, T8, FC5, FC6, FC3, FC4, C5, C6, FT7, FT8 **parietal:** P3, P4, P7, P8, CP5, CP6, CP3, CP4, P5, P6, TP7, TP8 **occipital:** O1, PO3, PO4, PO7, PO8, POz
Post-hoc – responders vs. non-responders post stimulation		
Positive cluster	5 – 17	**frontal:** F3, F4, F8, Fz, F1, F2, F5, F6 **central:** Cz, Pz, FC1, FC2, CP1, CP2, C1, C2, P1, P2, CPz **temporal:** C3, C4, T7, T8, FC5, FC6, FC3, FC4, C5, C6, FT8 **parietal:** P3, P4, P7, P8, CP5, CP6, CP3, CP4, P5, P6, TP7, TP8 **occipital:** O1, O2, PO3, PO4, PO7, PO8, POz, Oz

Note: Electrodes within frequency clusters grouped by brain areas.

11.2.2. Figures

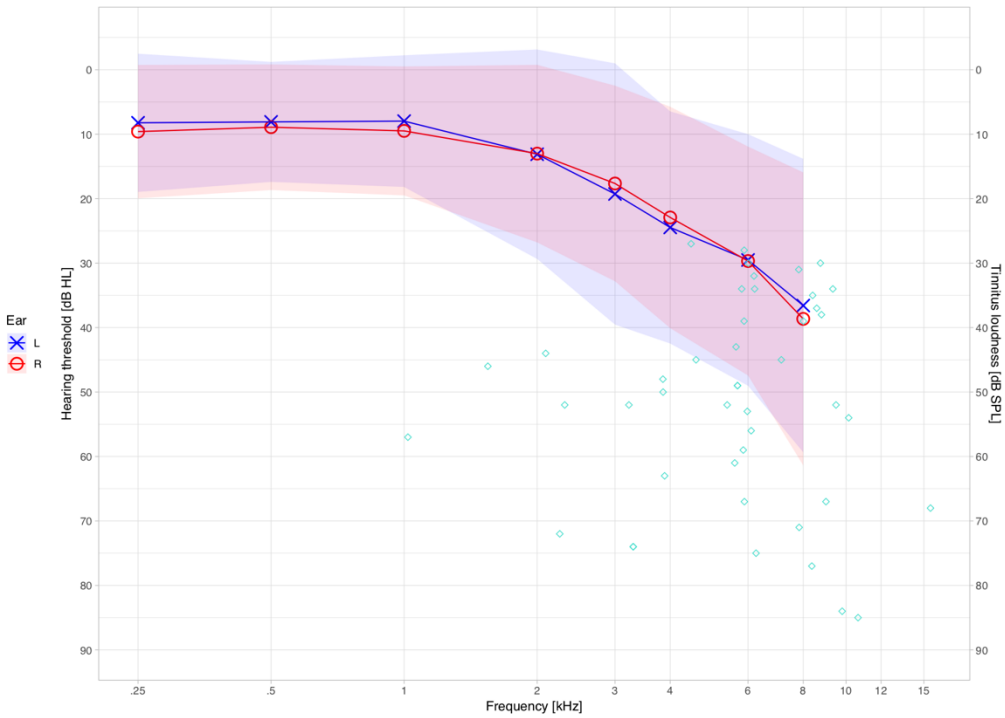

Figure S2. **Audiometry and Tinnitometry**.
L = left; R = right; HL = hearing loss; SPL = sound pressure level. Results of audiometric assessment for both ears together with tinnitus frequency and loudness. The frequencies of hearing loss overlap with tinnitus frequencies.

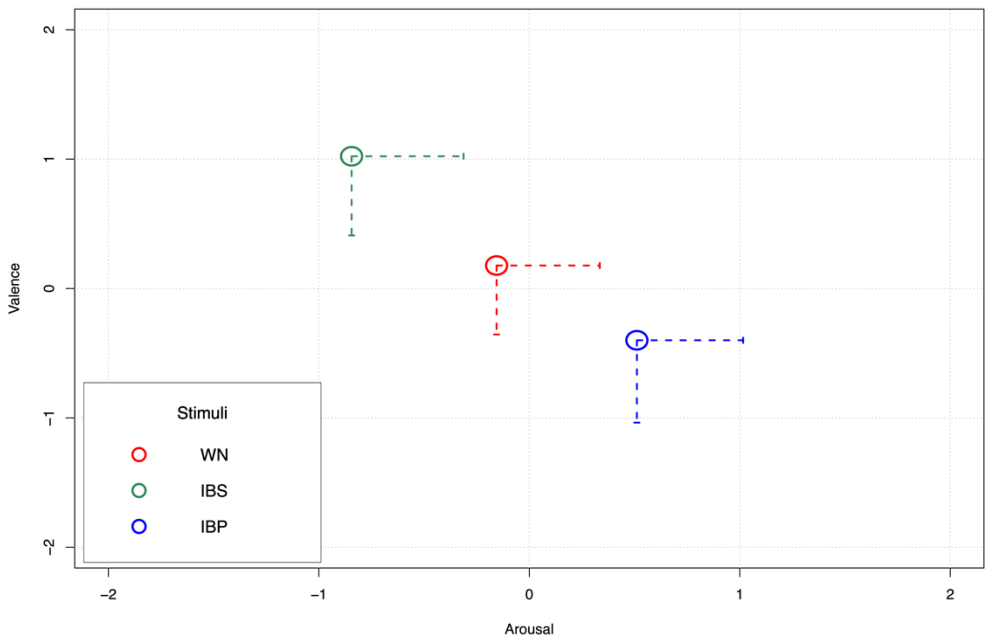

Figure S3. **Valence and arousal evaluation per stimuli**.
WN = white noise; IBP = individualized bandpass filtered white noise; IBS = individualized bandstop filtered white noise. The value 0 indicates a neutral stimuli evaluation (cf. section acoustic stimulation). Highest tolerability was found for stimulus IBS as exemplified by high valence and low arousal ratings. While stimulus IBP resulted in the lowest tolerability evaluation. Parentheses display 95% confidence intervals for valence and arousal evaluation of the three stimuli.

11.3. Supplemental material – study 4

11.3.1. Tables

Table S14.

Electrodes forming reliable, sham-controlled clusters – alpha responder

Subject	Left 1 Hz	Right 1 Hz	Left 10 Hz	Right 10 Hz	Left 20 Hz	Right 20 Hz
1	-	-	-	-	FP2, AF4	-
2	P7, TP7	-	PO7, O1	-	-	-
3	PO8, P8, P6, TP8; PO7, P7, O1	-	F8, F6; TP7, T7	-	-	-
4	O1, Oz	-	-	-	-	-
5	T8, TP8	-	-	-	Fp1, Fpz, AF3, AF7	-
6	P3, P5	-	-	O1, PO3, PO7, Oz	POz, Pz	-
7	-	-	PO3, POz, P3	O1, PO7; O2, PO8	-	PO3, POz, P1
8	-	-	TP7, P7; O1, Oz	O2, Oz, PO8, PO4, O1	-	-
9	FT8, T8, F8	-	Fp2, Fpz; F6, FT8	-	P5, PO3, PO7	-
10	-	-	AF4, F4	-	-	CP2, CPz
11	F4, F6	-	-	FP2, AF8	-	POz, PO3
12	-	-	-	PO4, O2, PO8, Oz	-	-
13	-	FPz, Fp1	Fp1, Fpz	-	-	-
14	P8, P6, P4, PO8, PO4, O2, P7, PO7, Oz, O1	-	-	-	P7, PO7	P8, PO8, O2
15	-	-	F7, AF7	-	-	-
16	-	-	O1, PO3	AF8, Fp2	-	-
17	-	PO7, O1, PO3	-	-	-	PO8, O2
18	-	PO4, O2, PO8	-	AF4, Fp2	PO8, O2; O1, PO3	-
19	F7, AF7	FCz, Fz, F1, FC1	-	-	-	F6, FT8, C6
20		-	-	-	-	-
21	-	-	-	-	-	-
22	-	-	O1, PO8, O2, Oz, PO7	-	-	-

Note: Electrodes forming a cluster are separated by “;”.

Table S15.

Electrodes forming reliable, sham-controlled clusters – gamma responder

Subject	Left 1 Hz	Right 1 Hz	Left 10 Hz	Right 10 Hz	Left 20 Hz	Right 20 Hz
1	-	-	Fp1, AF7	F8, FC6	FC5, F7	-
2	T7, C5, FC3	-	C4, C6	-	-	-
3	AF3, F5	T8, TP8	-	-	-	-
4	PO8, P8, O2; T7, FC5	-	-	-	-	-
5	-	-	TP7, T7	-	-	-
6	-	-	-	Fp2, AF8, AF4, F6	-	-
7	-	-	-	-	-	O2, PO8
8	-	-	Fp2, Fpz, AF4, Fp1, AF8, AF3	-	F7, F5, FT7, FC5, FC3	-
9	PO8, P8, P6	C6, CP6, TP8, C4	Fpz, AF3, Fp1	-	C5, TP7	-
10	C3, FC3	-	-	Fp1, AF7, F3, F5	F4, F6	Fp2, AF8
11	-	Fp2, Fpz	-	FC6, C4	-	-
12	-	-	-	-	-	Fp2, Fpz
13	CP5, C3	C5, C3, CP3	AF3, FC3, F3	P8, TP8, PO8	-	-
14	-	FT7, F7, T7	FC6, T8, FT8; FC5, FT7	-	F7, AF7	-
15	T8, C6	Fz, F1	-	-	-	-
16	-	-	AF8, Fp2	-	-	TP8, T8, P8, C6
17	-	-	FP1, AF7, AF3, AF8, Fp2, AF4	FCz, AF4, F2	-	TP7, P7, CP5
18	F4, F3, F1, F2, Fz, FC4	Fp2, AF8, F4	AF4, F4	-	Fpz, AF3	-
19	-	-	T7, FT7	Fp2, Fpz	-	-
20	F6, AF4, F4, F8	-	Fp1, F3, AF8, AF3, AF4, F6, FC3, Fp2	-	-	-
21	-	O1, PO7	-	PO8, P8	TP8, P8; Oz, O1	C2, CPz
22	FT8, F8	-	AF8, F8; FT7, F5, AF7, F7, F3, FC5	-	-	-

Note: Electrodes forming a cluster are separated by ";".

11.3.2. Figures

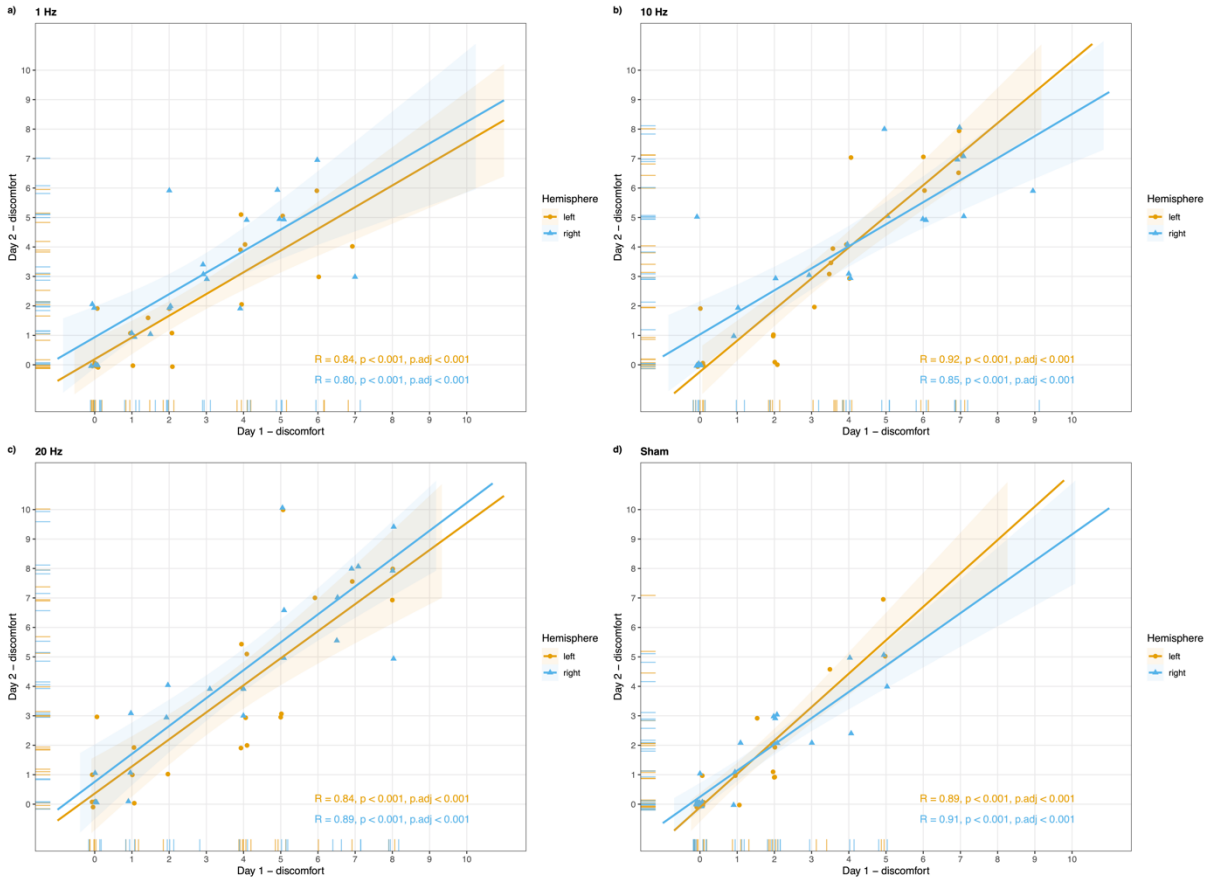

Figure S4. **Group-level reliability of TMS-induced discomfort**.
Spearman correlations of TMS-induced discomfort per rTMS protocol between the first and the second test session day are illustrated. Colored ribbons represent confidence intervals (95%). Significant positive correlations were observed for each applied rTMS protocol.

Affidavit

I, Stefan Schoisswohl born on 15th of September 1988 in Linz, Austria, hereby declare that I have written the present thesis without the unauthorized assistance of any third party and without the help of other resources and tools than the ones indicated. Data and concepts taken directly or indirectly from other sources are marked or cited accordingly. In particular, I have not made use of paid assistance of agency- or consulting-services for this thesis. The present thesis has not been submitted to any other examining authority in the same or similar form, neither in Germany nor abroad.

Wels, Austria; 12th of January 2021

Place; date

Signature of the doctoral candidate