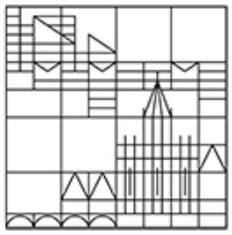
Riding the alpha wave – how auditory perception is shaped by oscillatory activity

Dissertation

zur Erlangung des akademischen Grades
des Doktors der Naturwissenschaften (Dr. rer. nat)

an der

Universität Konstanz



Mathematisch-Naturwissenschaftliche Sektion
Fachbereich Psychologie

vorgelegt von
Nadia Müller

Tag der mündlichen Prüfung: 05. Dezember 2011

1. Referent: Nathan Weisz
2. Referent: Thomas Elbert

Table of Contents

Danksagung

Zu Beginn dieser Arbeit ein kurzer Rückblick verbunden mit einem großen Dankeschön an alle, die dazu beigetragen haben, dass diese Arbeit in dieser Form entstehen konnte. An erster Stelle möchte ich gerne **Nathan Weisz** danken, der diese Arbeit betreut hat. Seine Begeisterung, wenn sich neue Ergebnisse abzeichneten, die damit verbundenen methodischen und inhaltlichen Diskussionen, die nicht selten in neuen Studienideen oder Theorien wie das Hirn funktionieren könnte endeten, waren eine gute Grundlage für diese Arbeit. Dabei schätzte ich es auch sehr, die Freiheit zu haben eigenen Ideen nachzugehen und selbständig zu arbeiten, bei Schwierigkeiten aber auch auf hilfreichen Input zählen zu können. **Thomas Elbert** möchte ich gerne für seine inspirierenden Ideen, kritischen Fragen und dem damit verbundenen anderen Blickwinkel danken. Außerdem für die Übernahme der Zweitkorrektur dieser Arbeit. Mein weiterer Dank gilt **Brigitte Rockstroh**, die maßgeblich zur angenehmen Atmosphäre im ZPR beiträgt und immer bemüht war den Wissenstransfer zwischen den Gruppen zu fördern. Danken möchte ich auch meinen direkten Kollegen, dem **aktuellen OBOB-Team** mit **Thomas Hartmann**, **Julian Keil**, **Hannah Schulz**, **Stephanie Franzkowiack**, **Sabine Jatzev** und **Teresa Übelacker**, die tagtäglich für Diskussionen fachlicher und auch nicht-fachlicher Art zu begeistern waren. Darüber hinaus möchte ich mich bei **Alexandra Müller** und **Astrid Steffen** fürs Korrekturlesen dieser Arbeit bedanken. Ein großer Dank gilt auch den Ex-OBOB-Teammitgliedern **Katalin Dohrmann**, **Winfried Schlee** und **Isabel Lorenz,** die die Anfänge meiner ‘ZPR-Karriere’ begleitet haben und mit denen nicht nur die Kaffeepausen etwas Besonderes waren.

Ursula Lommen, die ab der ersten MEG Messung bis zum gemeinsames Basteln an einem somatosensorischen Stimulationsgerät mit ihrer Offenheit für neue Ideen und Kreativität sehr viel möglich gemacht hat. **Christian Wienbruch** für die technische Unterstützung und kritischen Fragen. **Dagmar Moret**, die mit ihrem organisatorischen Talent Vieles vereinfacht hat. Dem ZPR-Team mit **Astrid Steffen**, **Anne Hauswald**, **Tzvetan Popov**, **Simon Hanslmayr, den OBOB-Leuten und Ex-OBOB Leuten**, **Sarang Dalal, Sarah Schulz, Hannah Adenauer** und vielen mehr die mich tagtäglich begleitet, inspiriert, ermutigt und zum Lachen gebracht haben. **Meinen Eltern und Geschwistern** Edgar, Steffi, Alexandra, Moritz, Patrick, Jakob und Emilie, mit denen ich auf den ersten (Alpha-) Wellen im Meer geritten bin, mit euch ist es nie langweilig! Und last but not least **Martin Voggel**, der meine Lieblingsabwechslung zur Doktorarbeit war; du warst ein Meister darin mich die Dinge klar sehen zu lassen, mich zur richtigen Zeit zum Lachen zu bringen und notfalls die echten Wellen im Atlantik aufzusuchen.

Zusammenfassung

Schon seit Beginn psychophysiologischer Forschung ist bekannt, dass identische Reize unterschiedliche neuronale Antworten und Perzepte auslösen können. Der momentane Zustand des Gehirns, der sich in einem spezifischen Muster neuronaler Oszillationen widerspiegelt, scheint dabei eine Schlüsselrolle zu spielen. In der Tat konnten Studien im visuellen und auch somatosensorischen System zeigen, dass insbesondere Oszillationen im Alpha Band (etwa 10 Hz), die Erregbarkeit von Hirnregionen bestimmen und systematisch unsere Wahrnehmung beeinflussen. Eine Abnahme von Alpha-Power wird dabei mit erhöhter Erregbarkeit in Verbindung gebracht und begünstigt die Wahrnehmung. Erhöhte Alpha-Power hingegen weist auf Hemmung der entsprechenden Hirnregion hin und unterdrückt Wahrnehmungsinhalte. Solch ein Zusammenhang konnte im auditorischen System noch nicht gezeigt werden und war Forschungsgegenstand der vorliegenden Arbeit. Dazu wurden die drei folgenden Studien entworfen.

Die erste Studie wurde mit dem Ziel konzipiert eine mögliche Top-down Modulation des auditorischen Kortex durch willentliche Aufmerksamkeit aufzudecken. Probanden wurden mittels eines visuellen Hinweisreizes gebeten, sich auf das rechte oder linke Ohr zu konzentrieren und nach einer kurzen Antizipationsphase am angezeigten Ohr Zielreize von Standardtönen zu unterscheiden. Es konnte gezeigt werden, dass Alpha-Power in der Hemisphäre, die bevorzugt den zu ignorierenden Ton verarbeitet, deutlich erhöht ist. Das passt zu Befunden aus anderen Modalitäten, die einen Zusammenhang zwischen erhöhter Alpha Power und der Hemmung von externen sensorischen Reizen feststellen konnten. Darüber hinaus war diese

Power Erhöhung mit einer verstärkten Synchronisation zwischen dem auditorischen Kortex und dem rechten Frontalen Augenfeld, das eine wichtige Komponente des räumlichen Aufmerksamkeitsnetzes darstellt, assoziiert. Die bedingungsspezifische Alpha-Power Modulation war bereits in der Antizipationsphase, also vor der auditorischen Stimulation zu beobachten und daher zweifellos durch Top-down Prozesse vermittelt.

Die *zweite Studie* befasste sich mit der Frage, ob durch eine direkte Modulation der auditorischen Alpha-Aktivität, auditorische Wahrnehmung verändert werden kann. Dazu wurde bei Patienten, die unter einem chronischen Tinnitus leiden, der auditorische Kortex mittels Transkranieller Magnetstimulation (TMS) stimuliert. Es wurde untersucht, ob durch die Stimulation gezielt Alpha-Power im auditorischen Kortex moduliert wird und inwiefern eine solche Modulation die Lautstärke des Tinnitus verändert. Eine deutliche Abnahme des Tinnitus ging tatsächlich mit erhöhter Alpha-Power im stimulierten auditorischen Kortex einher. Auch dieser Befund deckt sich sehr schön mit der Annahme, dass die Erhöhung von Alpha Power ein entscheidender Mechanismus ist, Wahrnehmungsinhalte zu unterdrücken.

Die *dritte Studie* wurde entworfen, um der Frage nachzugehen, ob und wie Alpha-Power moduliert wird, wenn gesunde Probanden eine auditorische Illusion wahrnehmen. Dazu wurde bekannte und unbekannte Musik durch kurze Rauschperioden unterbrochen. Bevorzugt im Kontext bekannter Musik entsteht eine kontinuierliche Wahrnehmung der Musik durch die Rauschperioden hindurch. Neurophysiologische Ergebnisse zeigen, dass Alpha-Power im auditorischen Kortex während Rauschperioden im Kontext bekannter Musik, also während der illusorischen Musik-Wahrnehmung,

deutlich reduziert ist. Diese Alpha-Power Reduktion weist auf eine Erhöhung von Exzitabilität im auditorischen Kortex hin und begünstigt die Wahrnehmung des illusorischen Perzepts. Wesentlich ist, dass in dieser Studie gezeigt werden konnte, dass *verringerte* Alpha-Power auditorische Wahrnehmung *begünstigte*. Auditorische Alpha-Power kann also in beide Richtungen moduliert werden, um Wahrnehmung zu unterdrücken oder zu begünstigen. Zusätzlich zu den auditorischen Alpha Power Modulationen, verstärkte sich die Kommunikation zwischen dem Parahippocampalen Komplex, der vermutlich mit der Musik assoziierte Gedächtnisinhalte speichert, und dem auditorischen Kortex. Durch diese Kommunikation könnte möglicherweise das Muster neuronaler Aktivität im hoch erregbaren auditorischen Kortex so geformt werden, dass eine Illusion von kontinuierlicher Musik entsteht.

Basierend auf diesen drei Studien kann man zusammenfassen, dass auditorische Wahrnehmung tatsächlich von oszillatorischer Alpha-Power im auditorischen Kortex abhängt. Außerdem, hängt die Modulation der Alpha-Power mit der Kommunikation zwischen dem auditorischen Kortex und nicht-auditorischen Hirnregionen zusammen, die spezifisch für verschiedene Wahrnehmungsinhalte oder Aufgaben ist (Netzwerk räumlicher Aufmerksamkeit, Gedächtnisnetzwerk). Diese Erkenntnisse passen zu Studien in andern Modalitäten wie dem visuellen System und erweitern den bedeutenden Einfluss bestimmter oszillatorischer Muster auch auf das auditorische System. Nicht zuletzt könnte die Bestimmung spezifischer oszillatorischer Muster sowohl in auditorischen als auch zwischen auditorischen und nicht-auditorischen Hirnregionen, die mit verbesserter Wahrnehmung oder pathologischen Zuständen wie etwa Tinnitus

zusammenhängen, als Basis für die Entwicklung effektiver Interventionen dienen.

Abstract

It is known since early psychophysiological research and an intriguing matter of fact that identical stimuli can elicit different neuronal responses and lead to varying percepts. The brain's current state, which is reflected in the pattern of ongoing neuronal oscillations, thereby plays a key role. Growing evidence in the visual/somatosensory modality shows that particularly the alpha rhythm (an oscillation at about 10 Hz) defines the excitability of a certain brain region and systematically impacts on perception. While the decrease of alpha power points to increased excitability that facilitates perception the increase of alpha power has been related to the inhibition of the accordant brain region resulting in an inhibition or gating of perception. For the auditory modality, however, no such association has been established yet. Three studies were designed to investigate whether also auditory perception is dependent on the modulation of auditory alpha oscillations.

The *first study* was carried out to examine the top-down modulation of the auditory cortex mediated by voluntary attention. Participants were visually cued to attend to either the left or right ear and after a short anticipation phase they had to distinguish target from standard tones at the respective ear. In line with the notion that an increase in alpha power reflects the gating of sensory information a prominent increase of low auditory alpha power in the hemisphere predominantly processing the to-be-ignored sound was found. The alpha power enhancement was further related to an increased synchronization between the strongly modulated auditory cortex and the right frontal eye fields described as key structure of the spatial attention network. Importantly, the condition-specific alpha power modulation in the auditory

cortex was already present during anticipation of the auditory stimuli and thus mediated by mere top-down processes.

These results led to another research question that is whether auditory perception is influenced automatically by bottom-up modulation of auditory alpha power. To address this within the *second study* the continuous perception of a phantom sound in tinnitus patients was altered by stimulation of the auditory cortex with Transcranial Magnetic Stimulation. The question was whether the perceptual changes are reflected in the modulation of auditory alpha activity. Strong *decreases* in tinnitus loudness were indeed related to increases in auditory alpha power at the stimulated site. This is in accordance with the notion that an increase of auditory alpha power is a crucial mechanism for gating auditory perception. The finding is further in line with the results of the first study that related increased auditory alpha power to a gating of external auditory stimuli.

The *third study* was designed to examine whether and how oscillatory alpha activity is modulated when an auditory illusion is generated in healthy students. Therefore, auditory oscillatory activity to invariant sounds embedded in familiar as well as unfamiliar music was compared. Based on the fact that perception of continuity is facilitated by experience, it was hypothesized that noise within familiar music would be more likely to elicit a continuous percept of music than noise within unfamiliar music. Results indicated that this was indeed the case and that during the illusory perception of music alpha activity was *reduced* in the auditory cortex. This finding points to an *increase* of auditory cortex excitability favouring the experience of an illusory percept. Importantly, in this study it was shown that a *decrease* of auditory alpha

power *facilitated* auditory perception emphasizing that auditory alpha power can indeed be modulated in both directions to either facilitate or gate perception. In addition to the auditory alpha power modulations, the auditory cortex increased its communication with the parahippocampal formation that likely stores the memory contents associated with the music illusion. It seems thus likely that neuronal activity in the highly excitable auditory cortex was shaped through the auditory-parahippocampal communication so that the illusion of continuing music was generated.

Based on the three studies it can be concluded that auditory perception indeed depends on oscillatory alpha activity in the auditory cortex. Furthermore, the modulation of auditory alpha activity is related to the communication between the auditory cortex and non-auditory brain regions that are specific for different percepts or tasks (such as the spatial attention network or memory network). These findings are consistent with and extend findings concerning the impact of specific oscillatory activity patterns on perception from other modalities like the visual or somatosensory to the auditory. Last but not least, determining the signatures in auditory and non-auditory brain regions that are associated with improved auditory perception or pathological conditions such as tinnitus will serve as a basis for the development of effective interventions.

Conducted studies and own research contribution

The studies of the current thesis were co-authored and supported by a number of colleagues. They are listed below together with my own research contributions.

Study 1: Lateralised auditory cortical alpha band activity and interregional connectivity pattern reflect anticipation of target sounds

Authors: Nadia Müller and Nathan Weisz

Published in *Cerebral Cortex*

I supported the planning and the design of the study, carried out the MEG measurements, performed the data analyses and drafted the manuscript.

Study 2: rTMS induced tinnitus relief depends on increases in auditory cortical alpha activity

Authors: Nadia Müller, Isabel Lorenz, Berthold Langguth and Nathan Weisz

Currently submitted (current status from 17 August 2011: 2nd major revision at *Brain*)

I recruited the patients, carried out the rTMS interventions, accomplished the pre and post MEG recordings and collected pre and post behavioural data. I did this for half of the patients (the other half was performed by Isabel Lorenz). Furthermore, I performed the data analyses and drafted the manuscript.

Study 3: You can't stop the music – reduced auditory alpha power and enhanced auditory-parahippocampal coupling facilitate the illusion of continuity during noise

Authors: Nadia Müller, Julian Keil, Jonas Obleser, Hannah Schulz, Thomas Grunwald, Hans-Jürgen Huppertz and Nathan Weisz.

I designed and implemented the experiment, ran the MEG recordings, carried out the intracranial recordings at the epilepsy centre in Zürich (EPI), performed the data analyses and drafted the manuscript.

Abbreviations

ANOVA Analysis Of Variance

dB Dezibel

DICS Dynamic Imaging of Coherent Sources

ECoG Electrocorticography

EEG Electroencephalogram

e.g. For example (Latin: exempli gratia)

ERD Event Related Desynchronisation

ERP Event Related Potential

ERS Event Related Synchronization

et al. And others (Latin: et alii)

fMRI Functional Magnetic Resonance Imaging

Hz Hertz

i.e. that means

lcmv linear constraint minimum variance

MEG Magnetoencephalogram

MRI Magnetic Resonance Imaging

ms milliseconds

NFB Neurofeedback

PDC partial directed coherence

PET positron emission tomography

PLI phase slope index

PLV phase locking value

rTMS repetitive Transcranial Magnetic Stimulation

TMS Transcranial Magnetic Stimulation

1.Introduction and Perspectives

1.1 Brain state dependent perception

Although early psychophysiological research showed that external stimuli with identical physical features elicit different neuronal responses and lead to varying percepts (Buzsáki 2006), neuroscientific research traditionally tries to identify the brain's typical response to external stimuli. Therefore, the responses are usually averaged to counteract the ubiquitous trial-to-trial variability of neuronal activity evoked by actually identical stimuli. Only recently research has begun to address the question on the origin of that variability. Intriguing evidence disclosed that whether or not a particular stimulus is perceived partly depends on the brain's current state. Buzsáki (Buzsáki 2006) postulated that 'stimulus-evoked activity gained by time-averaging of brain potentials or metabolic changes may reveal more about the *state of the brain* than about the physical attributes of the stimulus'. This notion further emphasizes that perception is a product of the stimulus *and* the brain's current state, but what signatures in neuronal activity could reflect such a 'state'?

Several EEG/MEG studies point towards a fundamental role of ongoing oscillatory activity that systematically impacts on perception and thereby defines how we perceive our environment (Buzsáki 2006, Klimesch et al. 2007, Mazaheri et al. 2010). Conceptually, oscillatory activity could thus be interpreted as the above-mentioned current "state" of a respective brain region. Neuronal oscillations can be uncovered by MEG or EEG recordings and reflect rhythmic fluctuations of the membrane potential, generated by the

summated excitatory post-synaptic potentials of several thousands of neurons (Lopes da Silva 1991). They are unambiguously defined by amplitude (power), frequency and phase. While amplitude describes the strength of the local field potential (number of synchronously active neurons), frequency refers to the fluctuation of the local field potential over time. The frequency of an oscillation depends on the intrinsic membrane properties, on the membrane potential of the individual neurons, and on the strength of synaptic interactions (Lopes da Silva 1991, Pfurtscheller & Lopes da Silva 1999). Phase defines the current position in a given cycle of the fluctuation and systematically affects the probability of a single neuron to fire (Jacobs et al. 2007). A consistent phase difference between two neuronal populations points to a systematic relation between them and has been interpreted as a measure of communication (Lachaux et al. 1999, Varela et al. 2001). The emergence of rhythmic fluctuations or oscillations requires specific network properties such as local neuronal assemblies are to some extent connected by long-range inhibitory interneurons (Buzsáki et al. 2004). Such long-range neurons can dynamically link the local assemblies (Pfurtscheller & Lopes da Silva 1999, Varela et al. 2001) so that the firing of single neurons becomes coordinated. On a macroscopic level these single coordinated neurons reflect an oscillation (Buzsáki 2006).

Despite the fact that neuronal oscillations are ubiquitous in the brain it is of great interest if they represent mere random fluctuations or, in contrast, systematically impact on how the brain processes external stimuli and thereby shape perception.

1.2 The outstanding role of alpha oscillations

Most investigations on oscillatory activity and its role on perception have been done in the visual system and revealed a significant correlation between the perception of a stimulus and different parameters (for example: power, phase) of ongoing *alpha* activity prior to stimulus presentation. Note, that the current thesis focuses on alpha *power*, while keeping in mind that growing evidence suggests that also 'alpha phase' might reveal intriguing aspects about the functional relevance of the alpha rhythm (Palva and Palva 2007). The alpha rhythm with a frequency of about 10 Hz was the first described human EEG pattern revealed by Berger in 1929. Alpha power is high during relaxed wakefulness, when the respective brain region is at rest and typically decreases when it processes a sensory stimulus. However, even at rest alpha amplitude fluctuates (Lopes da Silva 1991). Research has shown that the alpha rhythm is associated with the excitatory–inhibitory balance within respective sensory regions. Low alpha power reflects a state of high excitability and favours perception while high alpha power is related to an inhibitory state and gates perception (Klimesch et al. 2007, Mazaheri et al. 2010). This notion is mainly derived from studies on selective attention that have shown that modulations of ongoing alpha oscillations facilitate or inhibit visual processing (Fries et al. 2008, Klimesch et al. 2007, Rihs et al. 2009, Romei et al. 2008, Sauseng et al. 2005 & 2008, Thut et al. 2006, Ergenoglu 2004, van Dijk 2008). Similarly, alpha power in the somatosensory cortex has been shown to impact on somatosensory perception (Jones et al. 2010, Haegens et al. 2011). The alpha rhythm thus has a special role in mediating the excitatory-inhibitory balance in sensory systems and systematically

modulates perception. In the auditory system, however, such an association has not been established yet.

1.3 Alpha-like oscillations in the auditory cortex

Evidence exists that an alpha-like rhythm is also present in the auditory system. In 1997 Lethelä and colleagues found out that, similar to the visual or somatosensory system, also the auditory cortex exhibits an alpha-like rhythm (between 6.5–9 Hz) that decreases in power following auditory stimulation. This has been corroborated by data from epilepsy patients with electrodes implanted in the auditory cortex for stereotactical EEG (Weisz et al. 2011). The importance of auditory alpha power in perception has only recently gained in interest and its functional role has remained largely unexplored. Van Dijk and colleagues (2010) showed that alpha power in the left auditory cortex increases during working memory retention of pitches. A potentially functional relevance of auditory alpha power is further derived from studies on chronic tinnitus that show that patients who chronically perceive an illusory sound exhibit significantly less auditory alpha power than normal hearing controls (Weisz et al. 2005). However, evidence on the role of auditory alpha power for auditory perception is still rare. The main goal of the current work was thus to find out if also *auditory* alpha power is modulated systematically and if such a modulation has significant consequences on auditory perception. Such a finding would underpin the notion that auditory alpha activity reflects the current state of the auditory cortex and it would extend the knowledge about

the impact of alpha oscillations on perception from the somatosensory/visual modality to the auditory system.

1.4 Shaping of auditory alpha oscillations by non-auditory brain regions

Given that alpha oscillations fluctuate systematically, it seems relevant to find out how such a systematic modulation is initiated. Particularly in the visual domain it has been shown that higher-order brain regions mediate modulations of occipital oscillatory alpha activity (Capotosto et al. 2009). Electrophysiological research suggests that different neuronal assemblies communicate via phase synchronisation of oscillatory activity (Canolty et al. 2010, Varela et al. 2001; Womelsdorf et al. 2007). Thus, if auditory alpha power is indeed modulated systematically this modulation could depend on a specific synchronization pattern between the auditory cortex and non-auditory brain regions involved in respective top-down processes. The investigation of such networks was a further goal of the current work and was studied by examining phase synchrony between auditory and non-auditory brain regions. Thereby it could be revealed whether auditory and non-auditory regions communicate with each other in a condition-specific manner related to the auditory alpha power modulations. As future perspectives, the directionality of such a communication could be defined by approaches that allow for causal inferences. TMS experiments or different analysis approaches, such as the Phase Slope Index (Nolte and Müller 2010) or Partial Directed Coherence (Sameshima and Baccala 1999) would be conceivable for the investigation of such causal relationships.

1.5 Overview of studies

To shed light onto the question if and how auditory perception is shaped by oscillatory activity I accomplished three experiments. Based on assumptions derived from results on other modalities, this work focused on the investigation of top-down and bottom-up influences on macroscopically recorded oscillations in the *alpha* band. The first experiment was designed to study the top-down modulation of the auditory cortex by higher order networks - responsible for allocation of attentional resources - in absence of any auditory stimulus. Participants were visually cued to attend to either the left or right ear and after a one second interval had to distinguish target from standard tones at the respective ear. During the task brain activity was recorded with MEG. This design aimed at examining whether and how participants prepare the auditory cortex for optimal processing during the anticipation phase (facilitation of the to-be-attended and gating of the to-be-ignored sound). It was hypothesized that the auditory cortex is prepared by the specific modulation of auditory alpha power. In line with the notion that an increase in alpha power reflects the gating of sensory information it could be shown that low alpha power was increased in the hemisphere predominantly processing the to-be-ignored sound. Interestingly, this effect was only evident in the right auditory cortex pointing to a lateralisation of the auditory system in spatial attention. Further it could be shown that the condition-specific right hemispheric alpha power increase was related to a synchronisation of activity in the right auditory cortex with the right frontal eye

fields described as key structure (Corbetta and Shulman 2002) of the spatial attention network. Precisely, the right frontal eye fields were coupled to the strongly modulated right auditory cortex (attend right) and decoupled from it when it was not modulated (attend left). These findings are first evidence for an alpha rhythm in the auditory system having the potential to specifically gate auditory processing similar to processes in the visual modality. Furthermore, this gating is associated with the communication with higher order brain regions such as the frontal eye fields.

If thus 'pure' top-down processes alter auditory cortical oscillatory activity and if this modulation has an effect on perception, the next question follows: If we modulate oscillatory activity, do we automatically modulate auditory perception? For this purpose a second study was conducted that addresses if auditory oscillatory activity can be externally modulated via a brain stimulation technique and whether this impacts perception. Participants were patients reporting chronic tinnitus, thus perceiving a permanent illusory sound. Transcranial Magnetic Stimulation affects brain activity directly and is thus a promising method to modulate maladaptive oscillatory activity in early sensory areas of tinnitus patients (Weisz et al. 2005). The impact of five different stimulation parameters (including a placebo sham condition) that are currently tested for tinnitus treatment and are thus likely to modulate the tinnitus percept and the underlying pattern of oscillatory activity was investigated. By comparing the oscillatory activity pattern (measured with MEG) and tinnitus intensity before and after rTMS it could be examined if and how oscillatory activity is influenced externally by rTMS. The altered oscillation patterns could then be related to modulations of the tinnitus

percept. In line with former studies comparatively weak modulations of tinnitus loudness and oscillatory activity, partly due to a high interindividual variability, were revealed for the individual stimulation protocols (see study 2). Beyond this, a *strong decrease* in tinnitus loudness that was related to an *increase* in *auditory alpha* power at the stimulated side could be shown when selecting the individually most effective stimulation protocols. This again underlines the notion that modulations of auditory alpha power (as shown in the first study) reflect an essential process to gate auditory perception. Importantly, this time, inhibition in the auditory cortex was induced from bottom-up by rTMS and apparently led to a strong modulation of auditory perception reflected in a reduction of tinnitus loudness lasting for more then twenty minutes. As tinnitus-associated oscillatory patterns in the patients have been consolidated for years they are probably actively maintained by, for instance, attention processes. This is also reflected by data from the current study showing that an increase of the tinnitus sensation was related to alteration in a left-lateralised fronto-centro-parietal network, confirming the relevance of this network for tinnitus perception. The beneficial bottom-up induced changes in such a dynamic system are thus likely to be susceptible to top-down mechanisms attempting to recover the former dynamics. Such processes will have to be investigated in future studies with a focus on enduring network activities.

The third experiment investigated if and how oscillatory activity is modulated when an auditory illusion is generated in healthy students. Context-elicited modulations of oscillatory activity and their impact on perception were examined by comparing periods of pink noise embedded in familiar as well as

unknown music. Based on the fact that perception of continuity is facilitated by experience, the identical noise periods are hypothesized to be processed differently: Noise within familiar songs elicits a continuous percept of music while noise within unfamiliar music is processed as noise. MEG was recorded while participants were listening to the noise sections embedded in the music pieces. In addition to the MEG study, intracranial data from epilepsy patients in the EPI (Epilepsy Centre Zürich, EPI) were collected in order to compare and validate the MEG findings. Data show that during perception of illusory music alpha activity is *reduced* in the auditory cortex pointing to an *increase* of auditory cortex excitability that favours the experience of an illusory percept. This is in line with results from study 2 showing that an *increase* of alpha power *reduces* the perception of an illusory sound in patients perceiving a phantom sound. As a second finding it was revealed that the parahippocampal formation that stores the memory contents associated with the illusion increased its communication with the highly excitable auditory cortex and thereby putatively shapes neuronal activity in the auditory cortex so that an illusion of continuing music is generated. This is consistent with study 1 showing that an increased synchronization between the auditory cortex and crucial, non-auditory, brain regions is related to local auditory alpha power modulations. Importantly, the first two studies point to an alpha power increase during the gating of perception (to-be-ignored sound in study 1 and reduced phantom sound in study 2), while the third study indicates an alpha power decrease during the facilitation of perception (illusion of continuing music).

Based on the three experiments I would like to conclude that auditory perception indeed depends on the 'state' of the auditory cortex. This 'state' is reflected in local auditory alpha oscillations that are either top-down mediated through the communication with non-auditory brain regions or can be elicited from bottom-up by transcranial magnetic stimulation. Dependent on the task or experimental manipulation alpha power can be modulated in both directions to either facilitate (low alpha) or gate (high alpha) the auditory cortex resulting in specific consequences for auditory perception. The findings extend the role of alpha activity from the visual or somatosensory system to the auditory system. The modulation of alpha power thus seems to be a general mechanism for adjusting the excitability of sensory brain regions.

1.6 Perspectives for a systematic modulation of perception

Given the fact that auditory alpha power and auditory perception are closely related, one could imagine if we could systematically increase or decrease alpha power in the auditory cortex to either improve perception in cases of perceptual deficits or to inhibit, for instance, the perception of an undesired phantom sound. Importantly, auditory alpha power modulations were related to a communication with non-auditory brain regions (as, for instance, the spatial attention network or memory system). To modulate perception it is therefore essential to first identify a beneficial oscillatory pattern including a specific pattern in the auditory cortex (e.g. 'high auditory alpha power for the treatment of tinnitus') and a specific synchrony pattern with extra-auditory brain regions (e.g. 'high auditory–parahippocampal coupling to perceive a

music illusion'). To specifically facilitate or inhibit perception one could then try to directly interfere with the respective sensory cortex to provide the beneficial local oscillatory pattern, for instance, by Transcranial Magnetic Stimulation (as was tried out for the treatment of tinnitus). A potentially more lasting approach would be to induce the valuable oscillatory pattern through the network associated with the respective sensory cortex by, for instance, mental or cognitive training (e.g. neurofeedback, attention or memory training). Such a top-down approach could shape and strengthen important connections and feedback loops that could as a second step induce a beneficial state (facilitation or gating) in the respective sensory cortex putatively expressed in low or high alpha power. Most promising, however, would probably be a combination of both. Following this logic even complex phenomena such as tinnitus or pain perception could be tackled.

With respect to the above–described study on rTMS and tinnitus such a combined treatment approach could be realized as follows: Based on the fact that an alpha power increase in the stimulated auditory cortex was identified as the relevant mechanisms of action to reduce tinnitus such a treatment would on the one hand include the bottom-up modulation of auditory alpha activity by rTMS. Future clinical studies could identify the optimal rTMS protocol for increasing alpha activity in the temporal cortex in the individual patient in order to enhance clinical efficacy. On the other hand disadvantageous oscillatory activity in the auditory cortex could be tackled through the fronto-centro-parietal network possibly maintaining the tinnitus percept (see study 2).

As second example I would like to dwell on another clinically highly relevant phenomenon related to the somatosensory system: the perception of pain. Pain experience is known to be susceptible to top-down modulation and varies dramatically even when the activation of pain receptors (nociceptors) is similar (Ossipov et al. 2010). Based on the growing evidence on the role of alpha power for perception it seems thus likely that the modulation of pain is also mediated by alpha power in the respective brain region, putatively the somatosensory cortex processing the pain stimuli. This issue will be approached in the following study that I would like to shortly introduce. The aim of the study was to induce pain perception in normal healthy students by mere top-down context modulation in the absence of painful somatosensory stimulation. Participants were stimulated with short somatosensory pulses (another option would be to present stimuli with an intensity close to pain threshold) at the thumb of the left hand while they were watching a video. The video showed a left rubber hand that was stimulated by either a cotton bud (neutral condition) or a hammer (painful condition). Importantly, the rubber hand in the video appeared at exactly the same location as the real hand was felt. When the somatosensory and the visual stimulation are in synchrony the rubber hand in the video can be perceived as representing the own hand (rubber hand illusion; Ehrsson et al. 2005, Schaefer et al. 2006). Accordingly, it was hypothesized that particularly the participants who had the feeling to perceive their real hand on the screen (rubber hand illusion) process the somatosensory stimuli stronger when being touched by the hammer compared to the cotton bud. In such a realistic situation the visual context information (hammer vs. cotton bud) probably has a particular strong

influence. First behavioural results indeed show that the somatosensory stimuli are perceived with stronger intensity in the painful condition (‘hammer’) compared to the neutral condition (‘cotton bud’). One participant who had a very strong rubber hand illusion even described that every time when the hammer was on the verge of hitting her thumb she was frightened and had to constrain herself to not pull away her hand. These preliminary data (9 participants with about half of them perceiving a rubber hand illusion) show that strong top-down processes can modulate somatosensory perception, define how intense stimuli are perceived and possibly, in case of stimuli close to pain threshold, determine if they are perceived as painful or not. More behavioural data supporting this first impression and the analysis of alpha power in the somatosensory cortex together with the related top-down pain network (activated through visual input) could give further evidence on the components associated with pain perception. Based on this we could then specifically modulate brain activity (from top-down or/and bottom-up) in order to induce pain relief. With respect to the results on tinnitus perception high alpha power in the somatosensory cortex will probably be relevant to reduce pain perception. However, these hypotheses should be substantiated by further data and might rather serve as inspiration.

1.7 Overall conclusion

Based on the three studies conducted within the framework of the current thesis I can conclude that auditory perception depends on oscillatory alpha activity in the auditory cortex. The modulation of auditory alpha activity is

further related to a communication of the auditory cortex with non-auditory brain regions that is specific for different percepts or tasks (spatial attention network, memory network). These findings are consistent with studies in other modalities like the visual system and extend the impact of specific oscillatory activity patterns on perception also to the auditory system. With regard to the association between auditory perception and specific oscillatory patterns it seems feasible to positively influence disadvantageous oscillatory patterns. This would ideally include the modulation of unfavourable local oscillatory activity from bottom-up together with a top-down modulation through the related non-auditory brain regions. The described findings and resulting perspectives for future research go nicely with the notion that “a brain state can be regarded as a transient equilibrium condition, which contains all aspects of past history that are useful for future use” (Buzsáki 2006).

2. Studies on the role of auditory alpha power for perception

Study 1: Lateralised auditory cortical alpha band activity and interregional connectivity pattern reflect anticipation of target sounds

Introduction

EEG experiments investigating pre-stimulus allocation of visual-spatial attention suggest that the excitability of the visual cortex is modulated by decreasing or increasing ongoing alpha activity (8-12 Hz) (Klimesch et al. 2007). A decrease in alpha power (Event-Related Desynchronisation, ERD) is functionally related to active involvement of the underlying neuronal tissue that processes the upcoming stimulus whereas an increase in alpha power (Event-Related Synchronization, ERS) reflects active inhibition of the brain regions involved in processing distracting information (Foxe et al. 1998, Worden et al. 2000; Kelly et al. 2006; Rihs et al. 2007; Romei et al. 2008; Rihs et al. 2009; Jensen and Mazaheri 2010; Snyder and Foxe 2010).

Far less is known about similar processes in the auditory domain. In 1997 Lethelä and colleagues (Lehtelä et al. 1997) have shown that the processing of auditory stimuli involves a reduction of auditory alpha power. Despite this early study, only recently, accumulating evidence corroborates the existence of an auditory alpha rhythm as well as its functional role in auditory disorders such as tinnitus (Weisz et al. 2007, Weisz et al. 2011). However, to what extent the auditory alpha rhythm can be top-down modulated remains largely unexplored. To our knowledge, the only study investigating anticipatory alpha

power modulations in the *auditory cortex*, e.g. alpha modulations that are observed irrespective of the processing of auditory stimuli, is the one of Bastiaansen and colleagues (2001). The authors indeed showed an anticipatory alpha modulation in the auditory cortex, however, in only 2 out of 5 participants.

Assuming auditory alpha activity is indeed top-down modulated, the question arises: which brain regions are involved in this top-down control and how does communication with the auditory cortex take place? Most existing evidence is based on fMRI (and recently TMS) studies in the visual domain that consistently propose activation of frontal and parietal regions responsible for the allocation of spatial attention (Kastner and Ungerleider 2000; Corbetta and Shulman 2002; Fox et al. 2006; Serences and Yantis 2006; Slagter et al. 2007; Wu et al. 2007; Siegel et al. 2008; Capotosto et al. 2009). Corbetta and Shulman (2002) described the frontal eye field (FEF) and intraparietal sulcus (IPS) as core regions of the dorsal attention network mediating the top-down control mechanisms of attention. More recent neuroimaging studies postulate an activation of the dorsal attention network also during *auditory* spatial attention (Mayer et al. 2006; Voisin et al. 2006; Shomstein and Yantis 2006; Winkowski and Knudsen 2006; Salmi et al. 2009, Wu et al. 2007). In spite of strong evidence that fronto-parietal regions are involved in spatial attention in different modalities it is unclear how these fronto-parietal regions communicate with respective sensory cortices. Electrophysiological research suggests that different neuronal assemblies communicate via phase synchronisation of oscillatory activity (Canolty et al. 2010, Varela et al. 2001; Womelsdorf et al. 2007). We therefore hypothesise that fronto-parietal regions

phase-synchronise with the auditory cortex in a spatially-specific pattern related to the modulation of auditory alpha power.

We accordingly designed a dichotic listening experiment that visually cued participants to attend to either ear and to anticipate forthcoming auditory stimuli. Due to the simultaneous presentation of two concurrent sounds (one in the left and one in the right ear), we supposed that the auditory system has to inhibit sound processing at the unattended ear and to facilitate processing at the attended ear. According to this and because of the strong and preponderant contralateral anatomical connections in the auditory system (Evans 1982, Tervaniemi and Hugdahl 2003) we suggest two possible mechanisms that would support the processing of the attended sound. On the one hand the auditory cortex contralateral to the attentional focus (predominantly processing the attended sound) could be facilitated while on the other hand, and possibly even more decisive, the auditory cortex ipsilateral to the attentional focus (predominantly processing the unattended sound) could be inhibited. At this point it has to be mentioned that despite a contralateral dominance in monaural and binaural hearing it is known that the auditory cortex shows functional asymmetries between the hemispheres as e.g. in spatial sound localisation (Zatorre and Penhune 2001) and already within the ascending auditory system during dichotic listening (Della Penna et al. 2007). Notwithstanding these asymmetries and differences compared to the visual system, we nevertheless suggest that especially in anticipation of two *competing* sounds (binaural presentation at the left and right ear) a differential preparation of the auditory cortices depending on the anticipated ear is advantageous. Therefore, for the cue-stimulus phase we hypothesised

an asymmetric modulation of alpha power in the auditory cortex when attending to the left or right ear respectively. We furthermore assumed that fronto-parietal regions phase-synchronise with the auditory cortex, such that coupling with the modulated auditory cortex is enhanced.

Methods

Participants

15 participants reporting normal hearing and sight took part in the current study (9 male, 6 female). The mean age of participants was 25 years (range: 20 -28 years). According to the Edinburgh Handedness Inventory (Oldfield 1971), all participants were right-handed and free of psychiatric or neurological disorders according to the M.I.N.I. (Mini International Neuropsychiatric Interview, German Version 5.0.0). Participants were recruited via flyers posted at the University of Konstanz. The Ethical Committee of the University of Konstanz approved the experimental procedure and the participants gave their written informed consent prior to taking part in the study. After the experiment each participant received 15 € compensation for participation. Two participants had to be excluded because of too many artefacts in their MEG recordings (less than 60 trials after artefact rejection).

Task and stimuli

Participants were *visually* cued to attend to either ear, where they had to distinguish target from standard tones. The cue was an arrow pointing either to the left or to the right, which instructed participants to shift their focus to the designated ear. Following the presentation of a left cue, participants should have attended to the left ear and after the presentation of a right cue to the right ear. Arrows were always displayed in the middle of the screen. Auditory stimuli consisted of standard tones (90%) and target tones (10%). Standard tones were amplitude-modulated by either 45 or 20 Hz (carrier frequency: 655 Hz; stimulus duration: 800 ms; loudness: 50 dB above hearing level), whereas target tones altered their modulation frequency during presentation (from 45 Hz to 25 Hz and back to 45 Hz, from 20 Hz to 12.5 Hz and back to 20 Hz, Figure 1 displays such a target tone). Participants simultaneously listened to tones in both ears in a way that the 20 Hz modulated tone was presented to one ear and the 45 Hz modulated one to the other. The side of stimulation was randomly alternated and equally balanced between tones and ears. Target tones could only appear in the attended ear.

Procedure

Each trial commenced with a cross in the middle of the screen, upon which subjects had to focus their attention for 1 to 1.5 seconds. The arrow, randomly pointing to the right (100 trials) or left side (100 trials), subsequently appeared for 1 to 1.5 seconds. One to 1.5 seconds after cue onset subjects were exposed to the auditory stimuli. Immediately afterwards, participants

were asked by a question displayed on the screen if they had noted a target. Subjects had to respond to this with a right-hand button press. The intertrial interval (ITI) varied between 2.5 and 3.5 seconds. During the ITI, participants were encouraged to blink so that this could be avoided during task performance. The time intervals with the fixation-cross, the cue and the ITI randomly differed by a slight margin. The procedure of one trial is illustrated in Figure 1. In total, participants had to perform 200 trials during the course of the experiment.

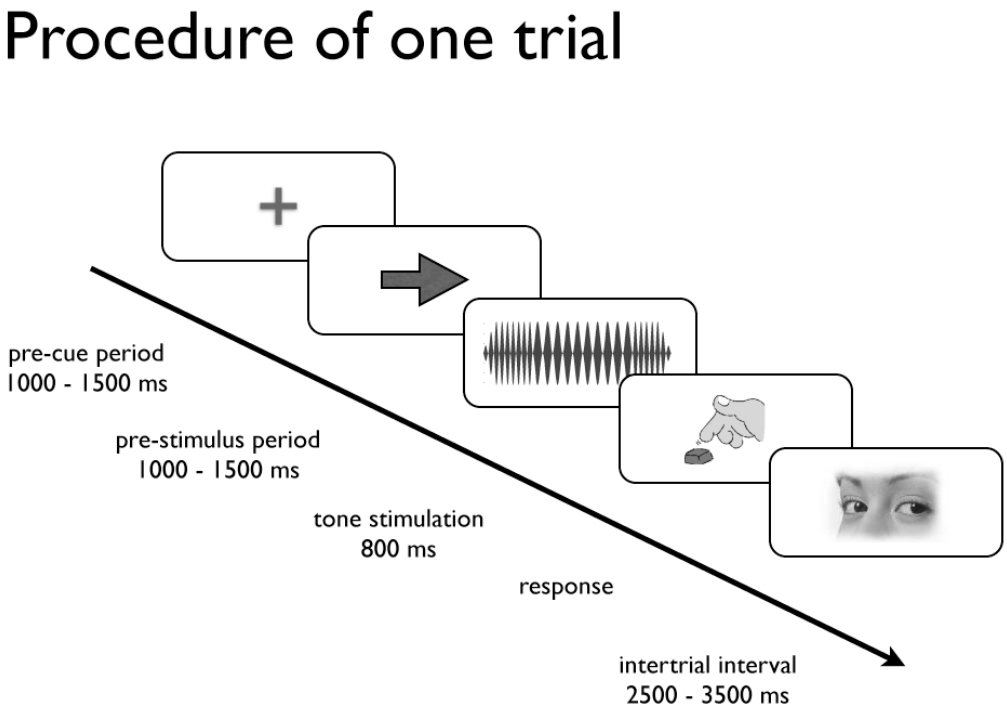


Figure 1: Depiction of one trial.

Data Acquisition

The experiment as well as the notation of events in the MEG data

acquisition was controlled using Psyscope X (Cohen et al. 1993) an open-source environment for the design and control of behavioural experiments (http://psy.ck.sissa.it/). Tones were generated outside of the magnetically-shielded chamber (ASG-BTI) and delivered to the participant's ear via flexible plastic tubes of the sound system. Instructions and visual stimuli were presented using a video projector (JVCTM, DLA-G11E) outside of the MEG chamber and projected onto the ceiling of the MEG chamber by means of a mirror system. Participants used a response pad to record their responses. The individual head shapes of all subjects were collected using a digitiser. The MEG recordings were accomplished with a 148-channel whole-head magnetometer system (MAGNESTM 2500 WH, 4D Neuroimaging, San Diego, USA), installed in a magnetically-shielded chamber (Vakuumschmelze Hanau) while participants lay in a supine position. MEG signals were recorded with a sampling rate of 678.17 Hz and a hard-wired high-pass filter of 0.1 Hz.

Data Analysis

Preprocessing

We analysed the data sets using Matlab (The MathWorks, Natick, MA, Version 7.5.0 R 2007b) and the Fieldtrip toolbox (http://fieldtrip.fcdonders.nl/). We separately extracted epochs of four seconds, including two seconds pre cue onset (baseline interval) and two seconds post cue onset (post-cue interval), and two seconds post-sound onset (during sound interval) from the continuously recorded MEG signal. This was done for each of the two

conditions, resulting in 100 trials for the attend-left condition and 100 trials for the attend-right condition for each of the three different time intervals. Trials were visually inspected for artefacts and we rejected those that were contaminated by blinks or muscle artefacts (trials for the different time intervals contained the same trials). After this procedure no trials with field changes larger than 3 pT were left. To ensure similar signal-to-noise-ratio across conditions the trial numbers were equalized for the compared conditions (attend left vs. right) by random omission.

Analysis of auditory alpha power modulations

As anticipatory auditory alpha activity could not be separated very well from pre-motor or parietal activity on sensor level we decided to define in a first step relevant auditory cortex regions as regions of interest (using the interval during sound stimulation with strong alpha power reductions elicited by the auditory stimuli). In a second step we then disclosed the time-frequency representation of the auditory regions of interest ('virtual electrodes') in the cue-stimulus interval and tested them for condition affects (attend left vs. right). In a last step we again localized the significantly modulated time-frequency interval (derived from the virtual electrodes) in the brain to assure that the main power modulation indeed arises from the auditory cortex.

Definition of auditory regions of interest

We defined the regions that exhibit strong alpha power modulations during

auditory stimulation (Lehtelä et al. 1997) as auditory regions of interest. We therefore analysed changes in spectral power for the interval during auditory stimulation first on sensor level and localized the modulated time-frequency interval then in the brain.

We estimated oscillatory power using a multitaper FFT time-frequency transformation (Percival 1993) with frequency dependent DPSS tapers (time window: $\Delta t=4/f$ sliding in 50 ms steps, taper: $\Delta f=.3*f$) for the baseline and during stimulus epoch and both conditions (attend left and right). We calculated power for 5 to 15 Hz in steps of 1 Hz and tested the obtained time-frequency power distribution for effects of activation (during sound) versus baseline. As a baseline, we chose the pre-cue interval when participants fixated a cross in the centre of the screen. As a next step, Dynamic Imaging of Coherent Sources (DICS) – a frequency-domain adaptive spatial filtering algorithm (Gross 2001) – was performed to identify the sources of the time-frequency effects. We calculated spatial filters for a 3-dimensional grid covering the entire brain volume (resolution: 1 cm) as well as the leadfields for each grid point for individual participants using a multisphere headmodel (Huang et al. 1999). For each grid-point, we constructed a common spatial filter from the cross-spectral density matrix of the MEG signal (activation and baseline) at the frequency of interest (9±3 Hz, as obtained from sensor analysis) and the respective leadfield (regularization: lambda=15%). We then applied the spatial filters to the Fourier-transformed data (multitaper analysis) for the frequency (9±2.5 Hz) and time window of interest and normalised the resulting activation volumes to a template MNI brain provided by the SPM2 toolbox (http://www.fil.ion.ucl.ac.uk/spm/software/spm2). We calculated

source solutions for the baseline period (550 ms to 100 ms pre-cue) and for the interval during stimulus presentation (300 ms to 750 ms following tone onset) for both conditions separately (attend left and attend right). We then baseline corrected source solutions by applying a voxel-wise t-statistic that tested the activation period against baseline. Regions with significant modulations compared to baseline were defined as regions of interest and the respective voxel with maximal power modulation in the right (MNI coordinates: 51 -21 22) and left auditory cortex (MNI coordinates: -61 -25 27) as voxels of interest for the virtual electrode analysis.

Spectral power changes in the pre-stimulus interval obtained from the auditory cortex

Time-frequency representations for the voxels of interest were calculated as follows: The raw and downsampled data sets were first projected into source space by multiplying them with the accordant spatial filters. Spatial filters were constructed from the covariance matrix of the averaged single trials at sensor level (latency: 400 ms sec pre-cue to 1 sec post cue onset, 5–15 Hz, lambda 15%) and the respective leadfield by a Linearly-Constrained Minimum Variance (LCMV) beamformer (Van Veen et al. 1997). Afterwards we calculated spectral power for the voxels of interest from 5 to 15 Hz in steps of 1 Hz using a multitaper FFT time-frequency transformation (Percival 1993) with frequency dependent DPSS tapers (time window: $\Delta t=4/f$ sliding in 50 ms steps, taper: $\Delta f=.3*f$). The obtained time-frequency power distributions for the right and left auditory locations of interest and the two attention foci were

baseline corrected (baseline: 400–100 ms pre-cue, relative change) and then tested according to a potential interaction between attention focus and hemisphere. We therefore subtracted the attend-right from the attend-left condition within the right and left auditory cortex and then compared these difference representations using a point-wise dependent samples T-statistic. We thereby preserved the frequency and time periods that were significantly modulated at a 'virtual electrode' in the right and left auditory cortex according to the attentional focus. We further extracted mean values from the significantly modulated time-frequency maps (averaged across the significant time-frequency window: 6–7 Hz, 50–650 ms) for each participant, condition (attend left vs. right) and ROI (left and right temporal cortex) and again statistically tested these values using a 2 x 2 ANOVA (condition X ROI). In order to better separate cue-evoked from genuine induced alpha modulations we additionally calculated cue-locked activity for both conditions and the left and right virtual electrodes by low-pass filtering the raw data (30 Hz) and averaging the single trials. We then performed a time-frequency analysis on the evoked responses (same parameters as for virtual electrode analysis), baseline corrected (baseline: 400–100 ms pre-cue, absolute change) the obtained time-frequency representations and again tested them for an interaction between hemisphere and attentional focus. We thereby obtained the cue-locked activity contributing to the above described time-frequency effect.

As a last step we wanted to validate that the hemispheric and attention specific alpha power modulation derived from the virtual electrode analysis has indeed its main origin in the auditory cortex. We therefore performed a

DICS (as for the during sound analysis) to identify the sources of the time-frequency effects. We calculated spatial filters for a 3-dimensional grid covering the entire brain volume (resolution: 1 cm). For each grid-point, we constructed a common spatial filter (baseline and activation; regularization: lambda 15%) from the cross-spectral density matrix of the MEG signal at the frequency of interest (6.5±2 Hz, according to virtual electrode analysis) and the respective leadfield (obtained from during sound analysis). We then applied the spatial filters to the Fourier-transformed data (multitaper analysis) for the frequency (6.5±1.5 Hz) and time window of interest and normalised the resulting activation volumes to a template MNI brain provided by the SPM2 toolbox (http://www.fil.ion.ucl.ac.uk/spm/software/spm2). Source solutions were calculated for the baseline (700 ms to 50 ms pre-cue) and the cue-stimulus period (50 ms to 700 ms post-cue) for both conditions separately (attend left vs. attend right). We then baseline corrected source solutions by subtracting the baseline values from the activation values (post-cue) and tested the two attention conditions (attend left vs. right) using a voxel-wise dependent t-statistic.

Phase synchrony analyses

In order to identify the brain regions functionally connected to the auditory cortex during anticipatory auditory alpha power modulations we calculated phase synchrony (Lachaux et al. 1999) between the reference voxel within the right auditory region of interest (voxel with strongest power modulation associated with the attentional focus, as obtained from pre-

stimulus alpha power analysis; MNI coordinates: 47 -18 23) and all other voxels. If the phase differences between two oscillators deviate from uniformity they are likely to communicate with each other whereas uniform distribution of phase differences indicate the independence of two oscillators. We first Fourier-transformed the sensor level data (multitaper analysis, latency post-cue interval: 100 ms to 650 ms post-cue, latency baseline interval: 650 ms to 50 ms pre-cue, 2–30 Hz), extracted the complex values containing phase information and transferred these complex values into source space by multiplying them with the accordant spatial filters. Spatial filters were constructed from the covariance matrix of the averaged single trials at sensor level (latency: 650 ms sec pre-cue to 1 sec post cue onset, 2–30 Hz, lambda 15%) and the respective leadfield by a Linearly-Constrained Minimum Variance (LCMV) beamformer (Van Veen et al. 1997). We thereby obtained complex values for each voxel and trial for the cue-stimulus and the baseline interval. We then converted these complex values into angles (radians) and calculated the difference between the reference voxel and all other voxels for each trial. This refers to the above mentioned ’phase difference’ between voxels. From these values we calculated the circular mean over all trials and employed a Fisher-Z transformation in order to assure normal distribution across subjects. In a final step, we subtracted the baseline values from the cue-stimulus values and thereby obtained relative phase locking values for each voxel and condition (attend left/right). These relative phase locking values quantify the average change of connectivity from baseline to the cue-stimulus phase.

For a more precise analysis of phase locking patterns we first identified a frequency band of interest in a data-driven manner. We defined this frequency band according to a global (e.g. averaged across all voxels) estimate of phase locking and its modulation according to to the relative power changes: We supposed that frequencies that show a modulation of the global phase locking values according to the different experimental conditions (attend left vs. right) are likely to be involved in top-down mechanisms that are related to the alpha power modulations in the different conditions. We thus estimated global phase locking values for both conditions (attend left/right) by averaging the relative phase locking values across all voxels. Such a procedure yields a measure that reflects large modulations of phase locking from baseline to activation and disregards precise anatomical information. We did this for frequencies from 2 to 30 Hz. We then performed a t-statistic across the global phase locking estimates for each frequency seperately and identified the frequencies that were specifically modulated according to the attentional focus (analogously to the right auditory alpha power modulation dependent on the attentional focus).

In a second step, we wanted to scrutinize the pattern of relative phase locking for the frequency band of interest (here: 5 Hz, see Results section), that means to disentangle the relative phase locking values into coupling (positive values, e.g. increased synchrony in cue-stimulus interval) and decoupling (negative values, e.g. decreased synchrony in cue-stimulus interval) and to disclose the main regions that (de-)couple with the right auditory reference voxel. We therefore focussed on the relative phase locking values (including the change in phase locking from baseline to the cue-stimulus phase for each

voxel, averaged across trials) at the frequency of interest and statistically tested these values according to the different conditions (attend left vs attend right) with a voxel by voxel paired Student's t-test. As a result we obtained statistical values for each voxel for phase locking with the right temporal reference voxel (attend right vs. attend left) and could thereby quantify the difference in phase synchrony between conditions. To correct for multiple comparisons we defined a minimum cluster size (minimum number of neighbouring voxels above a given threshold that are required for a significant cluster) with AlphaSim from the Afni Package (http://afni.nimh.nih.gov/afni/doc/manual/AlphaSim.pdf). We thereby preserved the main regions involved in coupling and decoupling with the auditory reference voxels and disregarded all voxels belonging to clusters with less than the minimum cluster size (770 voxels). Finally, we extracted the mean relative phase locking values from our region of interest (right FEF) for the two conditions seperately and tested them with the accordant Student's t-tests. Since the involvement of the IPS was not evident even without control for multiple comparison, we did not pursue any ROI analysis for this region. As the frontal eye fields have been associated with eye movements and also the planning of eye movements we wanted to rule out that potential differences in phase synchrony between conditions parallel visual cortical activity. We therefore repeated the described phase synchrony analysis with a reference voxel in the right FEF (MNI coordinates: 31, -14, 65) in order to exclude that any effects for the right FEF is paralled by coupling with primary visual areas.

Results

Behavioural Results

Over all participants and trials, subjects correctly identified 74 percent of the tones, indicating that the task was feasible (but still challenging). Participants showed the same behavioural performance for the 40 Hz modulated tones (mean ± standard deviation: 76 % ± 18) and the 20 Hz modulated tones (72 % ± 23). Likewise, attending to the left (73 % ± 20) or to the right ear (76 % ± 18) did not affect the respective response patterns. The corresponding student's t-tests statistically confirmed equivalence; both tests argue for the absence of differences between means (each $p > 0.5$). Mean reaction times were significantly shorter ($p<.001$) for the attend-left (mean: 940 ms, standard deviation: 240 ms) compared to the attend-right condition (mean: 1600 ms, standard deviation: 290 ms). It has to be noted, however, that responses were given *after* stimulus offset, i.e. speed was not a requirement of the task.

Alpha power decrease during sound stimulation

Time-frequency analyses showed significant alpha power decreases during sound processing compared to baseline for both conditions ($p < .05$). The alpha reductions at representative temporal sensors were most prominent from 6.5 to 11.5 Hz and from 300 to 750 ms post sound-onset. Alpha power decreases were localised in the vicinity of the primary auditory cortex (in the range of ~1 cm distance to BA 41, i.e. a deviance to be expected considering a grid-resolution of 1 cm and non-individual MRIs, MNI coordinates: left

auditory cortex –61 –25 27, right auditory cortex 51 –21 22). An illustration of the power changes during auditory stimulation averaged across participants is shown in Figure 2.

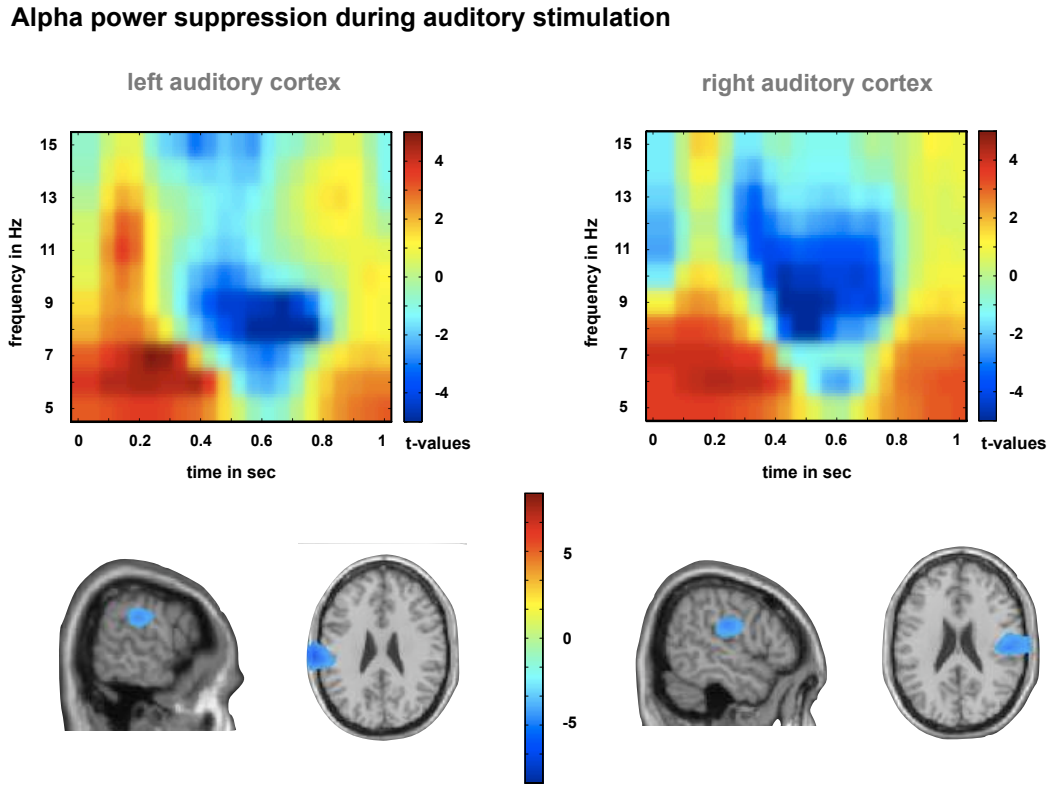


Figure 2: Upper panel: Time-frequency distribution during sound stimulation (stimulus onset at 0 sec) for a left and right representative temporal channel and expressed in t-values (during stimulus period compared to baseline). Alpha power reductions are visible from 300–750 ms post sound onset and between 6.5 and 11.5 Hz. Lower panel: Localisation of the significant time-frequency cluster in the brain. Modulations of alpha power are expressed in t-values (during stimulus period compared to baseline) and masked with a p-value <. 01. For both conditions (attend left and right) alpha power reduction was localised to the left and right auditory cortex.

Auditory alpha power modulation following the visual cue

Alpha power picked up by the auditory 'virtual electrodes' was modulated, already in anticipation of auditory stimuli following a visual cue. On a

descriptive level we observed two main processes that have to be differentiated: An immediate increase in low alpha power (5–8 Hz) that sustained up to 650–700 ms post cue followed by an alpha power decrease (8–12 Hz) peaking at the end of the post-cue period (interpretable interval up to about 900 ms post-cue). The early onset of the low alpha power increase, raises the notion that the visual cue could have lead to an auditory evoked response, that is potentially intermingled with genuine alpha activity. For this reason we also analysed the data in the time domain, pointing to an evoked auditory response following the visual cues especially in the right auditory cortex (see Supplementary Materials Figure 1). Interestingly, the right auditory cue-locked response differs between the two conditions in the first 150 ms (attend right elicits a *stronger* ERP than attend left). In an analysis described below we tested the influence this result may have had on the reported interaction when performing the time-frequency analysis on a single trial level. Due to overlap of the evoked and induced components in the early (< 500 ms) post-cue period, the later following alpha power decreases appear somewhat weaker. Note however that significant alpha decreases were noted in both hemispheres following a visual cue, particularly during the attend-right condition which on a descriptive level was more pronounced for the left auditory cortex (~8-13 Hz). See Figure 3 for a descriptive illustration of the results.

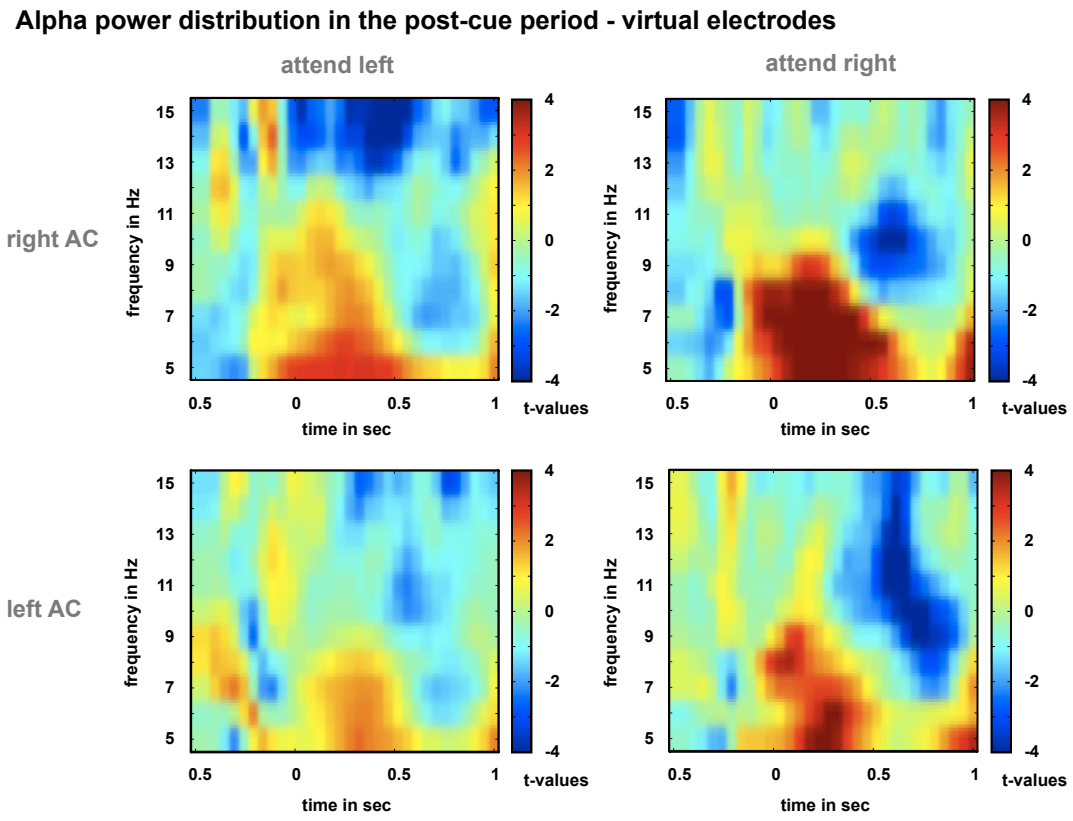


Figure 3: Time-frequency distribution in the cue-stimulus period at the left (lower panel) and right temporal (upper panel) virtual electrodes for the two conditions. Modulations of alpha power are expressed in t-values (cue-stimulus period compared to baseline, Cue appears at 0 sec). Two main processes are evident on a descriptive level: An immediate increase in low alpha power that sustained up to 650–700 ms post cue followed by an alpha power decrease peaking at the end of the pre-stimulus period (interpretable interval up to about 900 ms post-cue).

One of the major aims of our analysis was to investigate whether alpha power is differentially modulated for the left and right auditory cortex after a visual cue instructing the participants to attend to the left or right ear respectively. For this purpose we decided to test the interaction effect by subtracting the time-frequency representations between the attend left versus attend right condition for each hemisphere (left vs right auditory ROI) separately and then to compare these difference representations using a point-wise t-test. We

could indeed elucidate an interaction between hemisphere and attention focus ($p < .01$; see Figure 4 a and b) for 6–7 Hz and 50–650 ms post-cue with a transient weakening of the effect around 400 ms post-cue. The interaction is mainly due to a relatively stronger right auditory alpha power increase when attending to the ipsilateral right ear (post-hoc Student's t-test: $p < .05$; Figure 4c). Note that for this analysis we averaged over a period spanning early strong power increases and later power decreases, thus resulting in overall positive values. Importantly, this virtual electrode based effect (right auditory alpha power increase when attending ipsilaterally) was also located in the vicinity of the right auditory cortex (in the range of ~1 cm distance to BA 41, i.e. a deviance to be expected considering a grid-resolution of 1 cm and non-individual MRIs, MNI coordinates: 47 –18 23) with an independently calculated beamformer (DICS) approach (Figure 4d). The region strongly overlaps with the area exhibiting alpha power modulations during sound stimulation (peaks are in the range of ~5 mm distance).

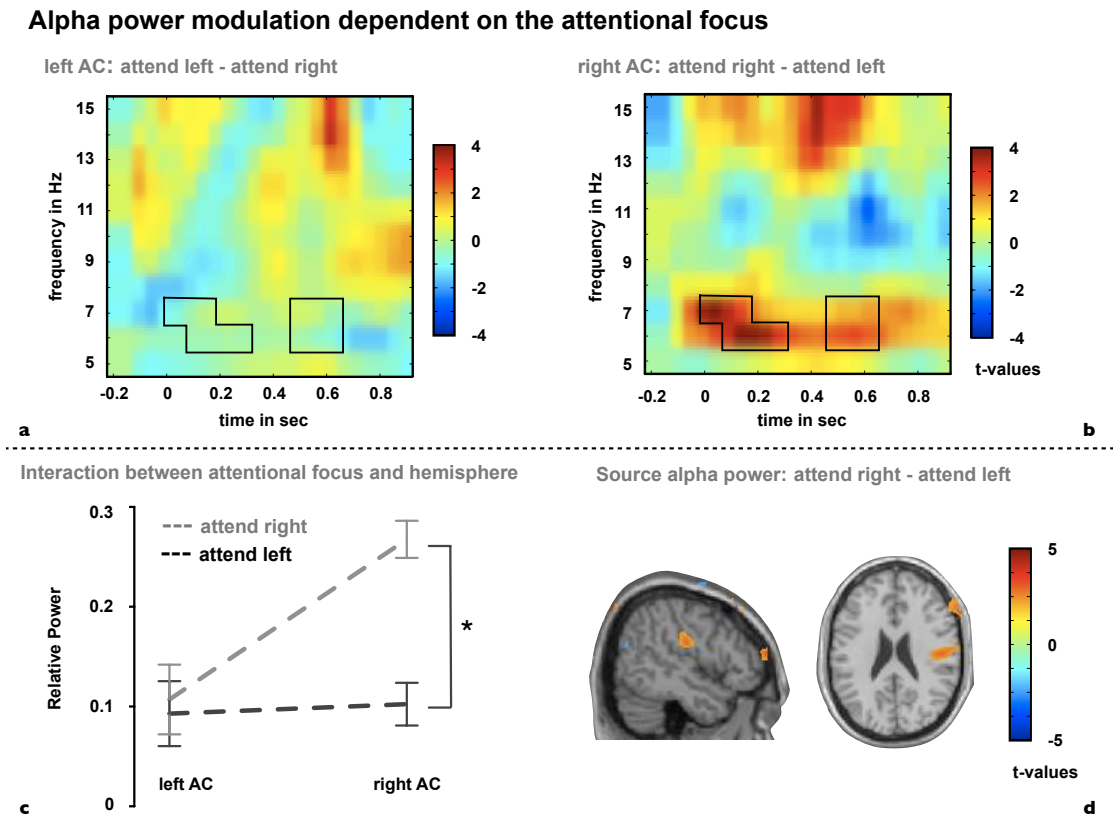


Figure 4: *a & b.* Alpha power modulation dependent on the attentional focus (upper panel). Shown are modulations for ipsilateral compared to contralateral attentional focus for the left (left side) and right (right side) auditory virtual electrodes. Modulations of alpha power are expressed in t-values (cue-stimulus period compared to baseline, cue appears at 0 sec). The black boxes show the significant time-frequency range according to the interaction between attentional focus and hemisphere. *c.* Interaction between attentional focus and hemisphere according to extracted mean values from the significant time-frequency interval. The interaction is mainly due to a strong increase in alpha power in the right auditory cortex when the ipsilateral right ear is attended (and the contralateral left ear to-be -ignored). *d.* Source localization of the contrast (attend right vs. attend left) for the time and frequency range of interest (50–650 ms, 6–7 Hz). Modulations of alpha power are expressed in t-values and masked by $p < .05$. The right auditory cortex (the region overlaps with the region exhibiting alpha power modulation during sound stimulation) shows a significantly stronger alpha power increase for the attend-right compared to the attend-left condition.

As stated above particularly for the right auditory cortex surprisingly strong evoked responses were observed following onset of the visual cue, which were stronger when attending to the ipsilateral ear. It is therefore possible that

the evoked response could have contributed to some extent to the interaction effect that we describe above and illustrate in Figure 4. A disambiguation of evoked and induced contributions is challenging, particularly in the face of single trial power increases. We therefore decided to perform the same interaction analysis described above on the time-frequency representations of the evoked responses. This analysis (shown in supplementary materials Figure 1) shows that the evoked response contributes significantly to the described interaction effect, however, only within a short time window (300–400 ms) and to a less strong extent. For this reason we conclude that the interaction effect is mainly due to a modulation of the induced responses.

Phase synchrony with the right auditory cortex

Global phase locking estimates with the right auditory cortex showed a marginally significant condition effect (attend left vs. right) for 5 Hz ($p = .06$). Based on this global estimate and in line with theoretical assumptions (von Stein et al. 2000; Lakatos et al. 2008) the 5 Hz band (theta) was defined as frequency band of interest for phase synchrony. In a second step, we calculated 5 Hz phase coupling of the right auditory reference voxel with all other voxels in the brain, thereby extracting the main regions that, compared to the baseline interval, increase or decrease their coupling with the right auditory cortex according to the attentional foci. Based on the dorsal attention network (Corbetta et al. 2002) the FEFs and the IPS were defined as regions of interest. The right auditory cortex was mainly coupled to a region in the vicinity of the right FEF (MNI coordinates: 31, -14, 65). This region

corresponds closely to the FEFs mentioned by Paus (Paus et al. 1996) and others (in the range of ~1-2 cm distance to FEF, i.e. a deviance to be expected considering a grid-resolution of 1 cm and non-individual MRIs). The observed relative coupling for the FEFs and the right auditory cortex was caused by a strong coupling when attending to the ipsilateral unattended ear (parallels the strong power modulation) and an equally strong decoupling when attention is directed to the contralateral attended ear (see Figure 5). Differences between coupling with the contralateral ear and decoupling with the ipsilateral ear were significant ($p < .01$). For the IPS no such a modulation was evident.

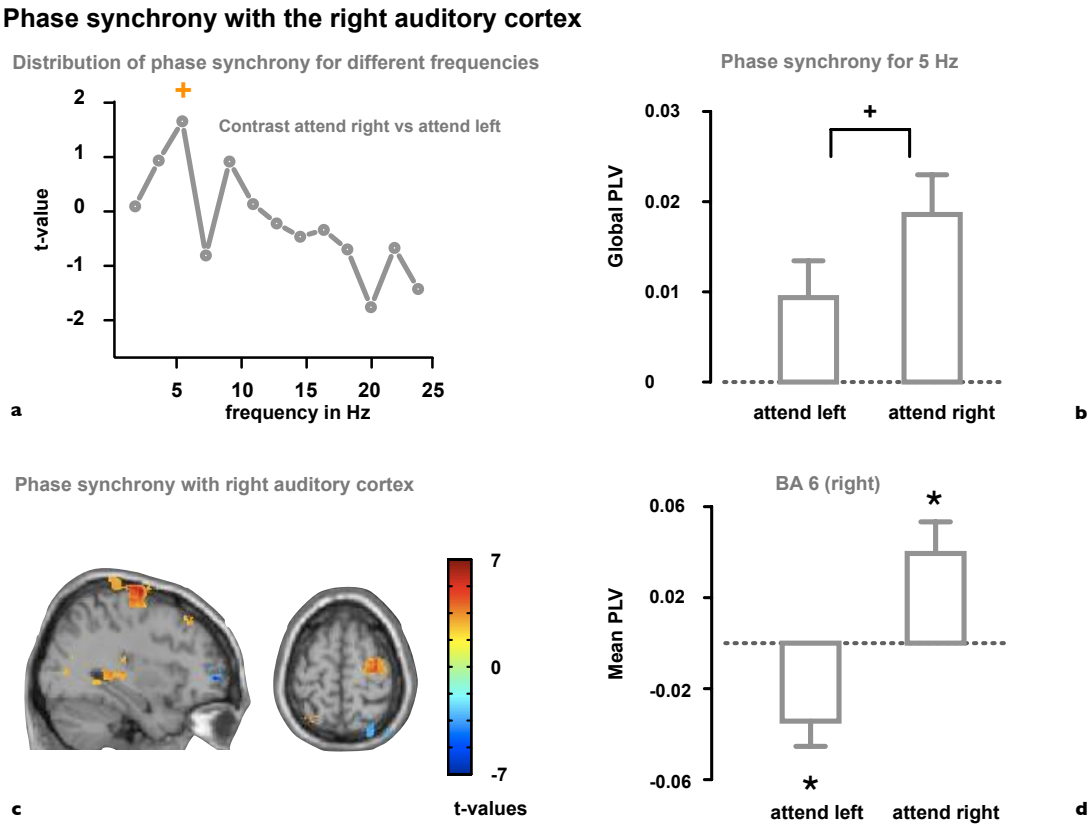


Figure 5: *a.* Condition contrast (attend left vs. attend right, right auditory cortex) of the global phase locking estimates for 2–30 Hz. The contrast is strongest for 5 Hz. *b.* Contrast of global estimates for 5 Hz. The effect is mainly driven by relative coupling with the unattended hemisphere. *c.* Modulations of phase synchrony with the right auditory cortex for the two

attention conditions (attend right vs. left), expressed in t-values and masked with a p-value <. 01. The main region showing significant differences of phase synchrony between conditions is an area in the vicinity of the right FEF (Brodman Area 6). *D.* Pattern of coupling and decoupling of the right FEF with the right auditory cortex according to the different conditions: The right auditory cortex is coupled with the right FEF when attention is directed to the ipsilateral unattended ear (this parallels the strong power modulation) and decoupled from this region when attention is directed to the contralateral attended ear (no significant power modulation).

Importantly, phase synchrony of the right FEF with the visual cortex (BA 17) did not differ between conditions (data is shown in the supplemental material, Figure 2 supplemental), therefore showing that the effects reported above cannot be seen as a side-effect of visual cortical activity.

Discussion

In the present work, we demonstrate for the first time that alpha power is modulated in the *auditory cortex* in anticipation of *auditory stimuli* indicated by a *visual cue*. Moreover, we could also show that this modulation happens in an asymmetric pattern depending on the focus of auditory spatial attention. We furthermore show that during the periods of auditory cortical alpha modulations, particularly the right frontal eye fields, couple with the strongly modulated right auditory cortex. In the following section, we elaborate upon the auditory power modulations and scrutinize the fronto-parietal regions associated with the auditory alpha changes.

Alpha power modulation in the auditory cortex

The analysis of alpha power during sound stimulation at the sensor level

points to alpha reductions most prominent between 6.5–11.5 Hz, which are localized to the right and left auditory cortex. This corroborates previous reports on small samples showing an alpha power reduction with sound stimulation (Lehtelä et al. 1997) and argues for the existence of an alpha generator in the auditory cortex. Here we would like to point out that we observed two consecutive processes during *anticipation* of the auditory stimuli: An early synchronisation of low frequency power (< 10 Hz) that is particularly strong for the right auditory cortex when the ipsilateral right ear is attended and a late and weaker desynchronisation of alpha power at about 9 Hz. According to recent literature the auditory alpha rhythm emerges in slightly different frequency bands (theta to common alpha band) depending on the task or method (Weisz et al. 2011). Our present results demonstrate early low frequency synchronisation followed by a higher alpha desynchronisation proximate to the expected earliest possible onset of the sound. The mentioned second process is descriptively weaker compared to the earlier modulations partly due to the fact that particularly for the right auditory cortex pronounced evoked activity could be observed following the visual cue (at around 150–250 ms). An early-evoked activation of the auditory cortex by visual stimuli is well documented in the literature (Schroeder and Foxe 2005, Pekkola et al. 2005, Schroeder et al. 2005, Ghazanfar and Schroeder 2006, Besle et al. 2008, Kayser et al. 2008, Raij et al. 2010) but has so far not been reported within the context of a spatial attention paradigm. Oscillatory activity, especially in the first 350 ms, thus likely reflects an overlay of cue evoked and induced oscillatory activity. However, two arguments can be given that indicate that this interesting evoked response can not explain in entirety the

effects observed in the single trial based time frequency analysis: 1) The asymmetric modulation of narrow-band low alpha power is sustained for more than 650 ms (see Figure 4b) considerably exceeding any effects reported on the level of evoked responses. 2) Importantly, a direct test of the relevant interaction effect on the evoked time-frequency data does not show effects to such an extent as seen for the single trial analysis (there is a significant interaction effect between 300–400 ms, but with much weaker intensity). We thus conclude that primarily genuine low alpha oscillations underlie the described asymmetric low alpha power modulation, which is functionally interpreted below. Nevertheless, the strong evoked responses as well as the - counterintuitive ipsilateral increase - following a visual cue raises interesting theoretical questions that they may play a crucial role in initiating specific oscillatory patterns for instance by cross modal phase resetting of low alpha oscillations (Klimesch et al. 2007, Lakatos et al. 2009, Thorne et al. 2011). Whether this could be the case or the evoked effects are just an independent response has to be clarified by further studies.

The fact that auditory cortical alpha activity is modulated by the presence of a *visual* cue already argues for top-down (anticipation) effects on auditory cortex. Exceeding this demonstration however, we could also show that low (6-7 Hz) alpha power is modulated differentially according to the attentional focus, particularly in the right hemisphere. We observed a prominent relative low alpha power increase in the right auditory cortex when anticipating an ipsilateral unattended sound while no such effect was evident when anticipating the contralateral attended sound (as stated above this interaction effect could not be observed to the same extent for the evoked

time frequency data). This interaction between hemisphere and attentional focus rules out non-specific processes related to alertness and points to the capacity of the auditory cortex to actively prepare for ear-specific sound processing in dichotic listening. An increase in alpha power, particularly in the hemisphere ipsilateral to the attentional focus predominantly processing the unattended sound, is consistent with several studies conducted mainly in the visual domain (Worden et al. 2000; Klimesch et al. 2007; Romei et al. 2008; Rihs et al. 2007, Jensen et al. 2010). Such an increase in alpha power has been interpreted as active gating of uncued locations (Worden et al. 2000, Jensen et al. 2010) and emphasized as important mechanism in realizing spatial attention by inhibitory top-down control processes, potentially even more crucial than alpha power decreases (Rihs et al. 2007). In the auditory modality, however, it has not yet been convincingly demonstrated that the excitability of the auditory cortex is altered in a top-down fashion. Kerlin and colleagues (Kerlin et al. 2010) demonstrated that the allocation of auditory attention to continuous speech is initiated by a lateralization of alpha power at parietal sites similar to the alpha modulations in visuospatial attention. Bastiaansen and colleagues (2001) were the first to show a reduction in *auditory* alpha power following an *auditory* cue; however, this effect only occurred in 2 of the 5 subjects who participated in the study reminiscent of the weak and late alpha power reduction we observed in the present experiment. Unfortunately, due to their design, they could not investigate interaction effects and rule out non-specific processes related to alertness. The interaction effects derived from the current study were mainly due to a *synchronisation* of *ipsilateral low* alpha power and pronounced the first 650

ms following cue-onset. We would like to mention that due to the fact that targets could only occur at the attended ear, we could not further investigate if the participants indeed attended to the cued ear or whether participants responded to any dichotic tone pair including an altered modulation frequency. Even though the finding of the specific low alpha modulations depending on the cued ear are very suggestive, future studies will also need to include the presentation of targets at the non-cued ear.

Right hemispheric dominance of auditory alpha power modulations

The condition-specific alpha power modulation was significantly stronger in the right compared to the left auditory cortex, driving the relevant interaction effect. We thus conclude that the right auditory cortex has a special role in auditory spatial attention and the processing of competing sounds at the left and right ear. This is not surprising, as many studies have provided evidence of hemispheric differences in auditory processing and hemispheric differences in spatial attention. It has been shown that the left auditory cortex primarily localises sounds in the contralateral right space, whereas the right auditory cortex is involved in computations for the whole space (Zatorre and Penhune 2001, Spierer et al. 2009). Thus the right auditory cortex seems to be less lateralised than the left auditory cortex. One could therefore assume that the right auditory cortex that is equally processing left and right ear stimuli should be down-regulated for the specific processing of an ipsilateral right ear sound (when left and right ear sounds are competing as in the present experiment). The left auditory cortex, in contrast, that processes sounds predominantly from the contralateral right ear does not

require such a modulation. Apart from these speculations, further experiments will help to elucidate asymmetries in the auditory system, which are already present during the anticipation of sounds.

Functional connectivity during pre-stimulus alpha modulations

Our data suggest that the observed asymmetric alpha power modulation in the right auditory cortex may be related to a relative coupling with the right FEFs. The FEFs show significant higher phase synchrony with the right auditory cortex when attending to the ipsilateral compared to the contralateral ear during periods of strong anticipation-related alpha modulations. In contrast, the FEFs are not differentially synchronised with the visual cortex so that the observed effects can not simply be explained by eye movements or visual attention, but point to a specific communication between the FEFs and the auditory cortex in the context of an auditory spatial attention task. We did not find any modulation in phase synchrony with the IPS. Worth noting is that we focus in our experiment on the regions of interest that exhibit *relative coupling* (Corbetta and Shulman 2002) in the 5 Hz band, keeping in mind that the entire system involved in auditory spatial attention probably comprises a larger network with a complex pattern of coupling and decoupling.

We presume that the FEFs are involved in top-down modulations of auditory cortical activity in the cue-stimulus period and communicate with these sensory regions by phase synchronising their respective oscillatory activities. Growing evidence suggests that neuronal communication among

distributed networks is realised through neuronal synchronisation (Singer 1999; Varela et al. 2001; Buzsáki and Draguhn 2004; Fries 2005; Schoffelen et al. 2005; Womelsdorf et al. 2007; Canolty et al. 2010). It has been proposed that attention may control cortical regions by synchronising of ongoing oscillatory activity (Engel et al. 2001; Salinas and Sejnowski 2001; Buzsáki and Draguhn 2004; Gross et al. 2004; Sauseng et al. 2006; Siegel et al. 2008; Gregoriou et al. 2009). According to these findings, our data show that neuronal activity in the auditory cortex is synchronised with the right FEFs during auditory spatial attention. The specific (de-)couplings were observed in the theta/low alpha band. Phase coupling of such lower frequency bands have been implied in long-range communication of distant brain regions (von Stein et al. 2000; Lakatos et al. 2008). However, the particular role of the 5 Hz band must still be substantiated by further data.

The FEF is one of the core regions corresponding to the dorsal attention network involved in visual (Kastner and Ungerleider 2000; Corbetta and Shulman 2002; Fox et al. 2006; Siegel et al. 2008) and, as more recently shown, in auditory spatial attention (Mayer et al. 2006; Voisin et al. 2006, Shomstein and Yantis 2006; Winkowski and Knudsen 2006; Wu et al. 2007; Salmi et al. 2009). This is in perfect accordance with our data, which demonstrate that the FEF is the main region specifically synchronised with the auditory cortex. The spatially-specific pattern of coupling and decoupling corroborates the functional relevance of the FEF for the spatially-specific auditory alpha modulations: the coupled ipsilateral auditory cortex shows a strong alpha power modulation in contrast to the decoupled contralateral auditory cortex with weak or almost absent alpha power modulation. Together

with the recently published TMS findings, which established a causal link between the activation of the FEF and auditory/visual spatial processing (Capotosto et al. 2009; Smith et al. 2009), it seems likely that the spatially specific auditory alpha power increase is mediated by a spatially specific synchronisation with the FEFs. Whether, however, the FEFs indeed modulate auditory cortical alpha power in a top-down manner must be tested in a future study using an approach (e.g., TMS) that allows for causal inferences.

To conclude, we emphasise that the present data goes significantly beyond the current knowledge on how auditory spatial attention in anticipation of auditory stimuli is implemented in the brain. We demonstrate that the implementation of auditory spatial attention in anticipation of auditory stimuli relies: 1) on a spatially-specific synchronisation between the FEF and the auditory cortex, such that coupling with the auditory cortex ipsilateral to the sound is enhanced and coupling with the auditory cortex contralateral to the sound is reduced; and 2) on the specific adjustment of auditory cortex sensitivity by gating actively the processing of irrelevant information (reflected in the increase of ipsilateral auditory alpha power).

Study 2: rTMS induced tinnitus relief depends on increases in auditory cortical alpha activity

Introduction

Tinnitus is defined as the subjective perception of a sound in the absence of any physical sound source. If persisting longer than a certain amount of time, conventionally between six and twelve months, it is usually regarded as 'chronic', reflecting clinical experience that the phantom sound will persist. Chronic tinnitus is a common phenomenon with a prevalence of 5-15% of the population in western societies (Eggermont and Roberts, 2004; Shargorodsky et al., 2010). In 1-3% of the population, tinnitus is associated with severe distress including psychiatric problems (e.g., depression), sleep disturbances, concentration problems or work impairment (Eggermont and Roberts, 2004). To date, there is no effective treatment that reliably eliminates tinnitus (Eggermont and Roberts, 2004), partly because the processes that generate and maintain tinnitus and its associated problems are not completely understood. A broad consensus, however, is that tinnitus is generated in central brain structures rather than in the peripheral auditory system. Evidence comes from clinical studies showing that the tinnitus percept persists even after transection of the auditory nerve fibres (Baguley et al., 2002; Zacharek et al., 2002).

In most cases, tinnitus is associated with a damage of hair cells in the inner ear (Rajan and Irvine, 1998; Salvi et al., 2000), resulting in pathological neuronal activity in central structures (Jastreboff, 1990; Weisz et al., 2005; Ashton et al., 2007; Roberts et al., 2010). Various neurophysiological

processes at different levels of the auditory system that are elicited by hearing loss have been suggested as being involved in the generation of tinnitus (Roberts et al., 2010). Hearing loss, for instance, results in a loss of inhibition and a reorganisation of the tonotopic map (Dietrich et al., 2001, Eggermont and Roberts, 2004). Studies in animals and humans demonstrate that the tinnitus sensation is associated with hyperactivity in subcortical and cortical auditory brain structures. This hyperactivity is reflected in an enhanced spontaneous firing rate (Noreña and Eggermont, 2003; Kaltenbach, 2006; Mulders and Robertson, 2009), elevated bursting activity (Noreña and Eggermont, 2003; Finlayson and Kaltenbach, 2009) and increases in neural synchrony that have been shown to correspond closely to hearing loss (Seki and Eggermont, 2003). Roberts et al. (2010) postulate that, among these processes, the increase in neural synchrony seems to be most relevant for the actual generation of tinnitus as it has the potential to impact postsynaptic targets and recruit cortical and downstream neurons into a tinnitus percept. The role of altered synchrony in tinnitus is strongly supported by studies that report changes in oscillatory brain activity associated with tinnitus (Ashton et al., 2007; Weisz et al., 2007; van der Loo et al., 2009; Ortmann et al., 2011). While oscillatory activity in the so-called alpha band (8-12 Hz), which has been related to inhibitory processes (Klimesch et al., 2007), is reduced in the auditory cortex of tinnitus patients (Weisz et al., 2005), power increases were found for low frequencies in the delta (Weisz et al., 2005) to theta range (Llinas et al., 1999; Ramirez et al., 2009; Moazami-Goudarzi et al., 2010) and in gamma power compared to normal hearing controls (Ashton et al., 2007; Weisz et al., 2007; van der Loo et al., 2009).

A promising treatment approach for chronic tinnitus is transcranial magnetic stimulation (TMS) (Kleinjung et al., 2007; Langguth et al., 2008), as this affects brain activity directly, thereby holding the potential to influence abnormal ongoing brain activity related to tinnitus. Particularly in its repetitive form (rTMS; Pascual-Leone et al., 1994; Chen et al., 1997), it has been shown (mostly in the motor system) that stimulation-induced changes of excitability outlast the period of stimulation. A growing number of studies indeed point to tinnitus relief after a series of ten rTMS sessions (for an overview see Plewnia, 2010), with effects lasting for up to four years (Khedr et al., 2009). However, the effects show great interindividual variability (Londero et al., 2006; Langguth et al., 2008) and only moderate effect sizes (Kleinjung and Langguth, 2009). Only few studies have investigated the effects of rTMS on auditory cortical activity in tinnitus sufferers and which aspects of these modulations are relevant for tinnitus relief. In a previous study, we were able to demonstrate that various forms of single session rTMS (particularly cTBS, iTBS and 1 Hz rTMS) could reduce the auditory Steady State Response (aSSR), which is in turn correlated with subjectively perceived tinnitus loudness (Lorenz et al., 2010). In the context of the same study we also collected resting MEG activity. To date, no published reports have investigated the impact of rTMS on spontaneous oscillatory brain activity in tinnitus patients - a potentially fundamental element in the generation of tinnitus (Weisz et al., 2005; Roberts et al., 2010). In order to better understand the pathophysiology of tinnitus and also to systematically advance tinnitus therapies, it is essential to know if and how oscillatory brain activity in tinnitus patients is modulated by rTMS and what changes in oscillatory activity are

crucial for tinnitus suppression. With the current data we are able to show that successful rTMS mainly leads to an increase in alpha activity in the auditory cortex, thus supporting the relevance of alpha activity for tinnitus (Weisz et al., 2005).

Methods

Participants

Ten patients with chronic tinnitus participated in the current study (7 males, 3 females). The mean age of the participants was 49.8 years (range: 21 - 70). Patients were recruited via advertisements in the local newspaper and flyers posted at the University of Konstanz. Tinnitus severity was assessed with Hallam's (Hallam et al., 1988) Tinnitus Questionnaire (*Tinnitus-Fragebogen*; Goebel and Hiller, 1994), revealing a mean score of 29.9 (range: 8 - 59). Half of the patients reported unilateral tinnitus (4 with left-sided tinnitus, 1 with right-sided tinnitus), while the other half indicated having perceived the tinnitus bilaterally. We only included patients with a maximum tinnitus duration of four years, as the impact of rTMS on chronic tinnitus declines with longer tinnitus duration (Kleinjung et al., 2007). All patients were informed about the content of the study as well as the potential risk factors and underwent a thorough anamnesis concerning potential contraindications for TMS (previous personal or family history of epileptic seizures, cardiac pacemaker, pregnancy, neurodegenerative diseases, brain injuries). Furthermore, patients with psychiatric or neurological disorders according to the M.I.N.I. (Mini International Neuropsychiatric Interview, German Version 5.0.0) and with anticonvulsant or tranquilizer medication were excluded from the study. The

Ethical Committee of the University of Konstanz approved the experimental procedure and the participants gave their written informed consent prior to taking part in the study.

Experimental design

Patients underwent five sessions of rTMS, including the measurement of tinnitus loudness and brain activity with MEG before and after rTMS. In the five sessions, five different rTMS protocols were applied, with a minimum interval of one week between sessions and using a randomized, single-blind, placebo-controlled design. For an overview of the study design, see Figure 1.

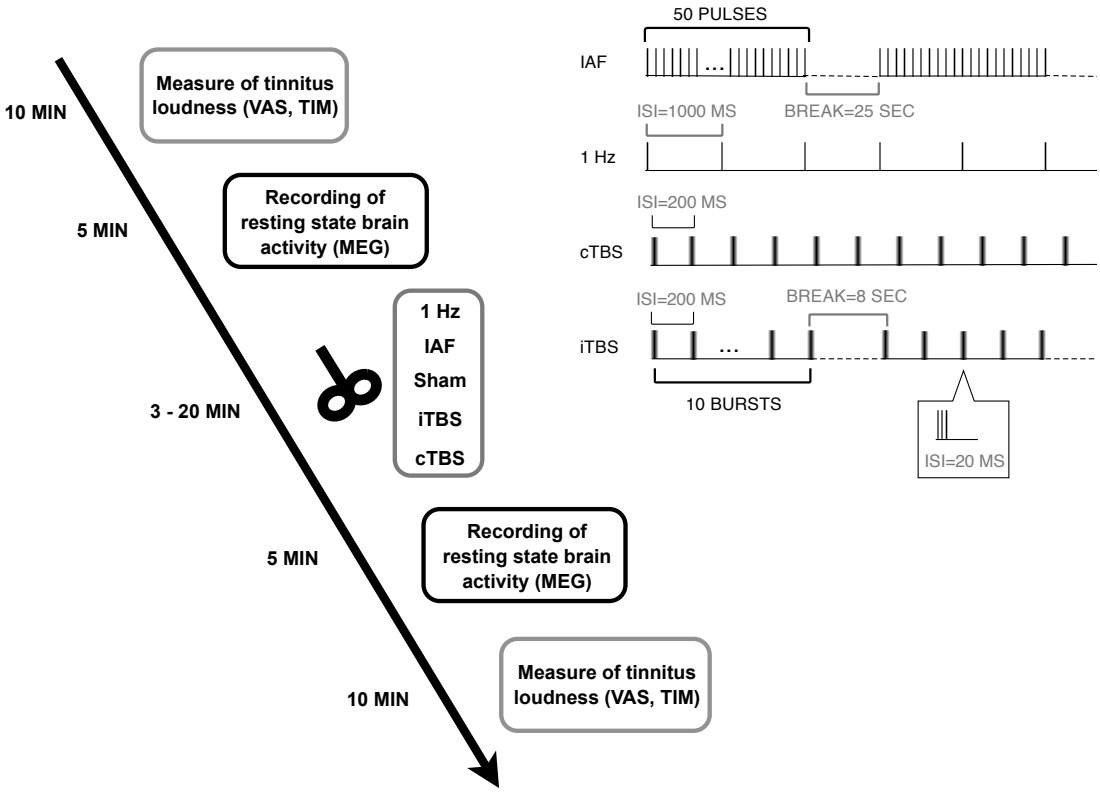


Figure 1: Experimental design. Patients underwent five sessions with five different rTMS protocols (including sham). In each session, tinnitus loudness

and oscillatory brain activity were measured before and after rTMS. The right upper panel illustrates the different stimulation protocols.

Measurement of tinnitus loudness

Before the first and after the second MEG recording, patients were asked to match the loudness of their tinnitus to a reference tone of 1 kHz (tinnitus intensity matching; TIM). This procedure considers the absolute hearing threshold of the 1-kHz tone so that the matched tinnitus intensity is expressed in 'sensation level'. Additional to this psychoacoustic assessment, the patients estimated their perceived tinnitus loudness on a visual analogue scale (VAS) ranging from 0 ('not loud at all') to 10 ('extremely loud').

Data Acquisition with MEG

The MEG recordings were carried out using a 148-channel whole-head magnetometer system (MAGNESTM 2500 WH, 4D Neuroimaging, San Diego, USA) installed in a magnetically shielded chamber (Vakuumschmelze Hanau). Prior to the recording, individual head shapes were collected using a digitiser. Participants lay in a supine position and were asked to keep their eyes open and to focus on a fixed point on the ceiling during the recording. The recording time was five minutes. MEG signals were recorded with a sampling rate of 2034.51 Hz and a hard-wired high-pass filter of 0.1 Hz. MEG measurements were conducted before and after TMS. The time interval between the end of the TMS session and the start of the second MEG recording did not exceed five minutes.

Brain stimulation with TMS

TMS stimulation (biphasic magnetic pulses) was administered with a figure-of-eight coil (coil winding diameter 2 x 75 mm; Magnetic Coil Transducer C-B60, Medtronic) connected to a MagPro X 100 TMS stimulator (Medtronic A/S, Skovlunde, Denmark).

Five different stimulation protocols were applied in randomized order over five sessions separated by at least one week: 1-Hz rTMS (1 train with 1000 pulses, frequency 1 Hz), individual alpha frequency rTMS (IAF; 20 trains with 50 pulses and 25 seconds inter-train interval, peak frequency ranging between 8 and 12 Hz), continuous theta burst stimulation (cTBS; 200 bursts at a frequency of 5 Hz with bursts consisting of 3 pulses at 50 Hz), intermittent theta burst stimulation (iTBS; 10 trains of 10 bursts at a frequency of 5 Hz with bursts consisting of 3 pulses at 50 Hz and an 8 seconds inter-train interval), and a placebo sham stimulation (45° coil angulation, applying the IAF protocol). Individual alpha frequency was defined as the peak of the power spectrum (between 8 and 12 Hz) at temporal sensors in the first MEG recording. For an illustration of the different protocols see right upper panel of figure 1. The patients were blind to the TMS condition. The intensity of the stimulation was adjusted according to the resting motor threshold (RMT) —a common procedure in TMS studies (Pridmore et al., 1998). RMT was measured by delivering single pulses at the optimal site over the motor cortex and defined as the lowest stimulation intensity required for producing visible hand muscle contractions in at least five out of ten trials. For 1-Hz rTMS, IAF,

and sham stimulation, intensity was set to 110% of the RMT and for iTBS and cTBS to 80% of the RMT (according to Huang et al., 2005). To prevent hearing damage caused by the loud clicking sound of the TMS device, patients were required to use earplugs. Patients were seated in a comfortable chair while the TMS coil was fixated with a mechanical arm. The handle of the coil always pointed upwards. In case of right-ear or bilateral tinnitus, the coil was placed over left Heschl's gyrus by moving 2.5 cm upwards from T3 on the line between T3 and Cz and then 1.5 cm perpendicularly in a posterior direction, analogously over right Heschl's Gyrus in case of left-ear tinnitus. This procedure has been proven to reliably position the TMS coil over the auditory cortex (Langguth et al., 2006).

Data analysis

Preprocessing

We analysed the data sets using Matlab (The MathWorks, Natick, MA, Version 7.5.0 R 2007b) and the Fieldtrip toolbox (Oostenveld et al., 2011). We separately extracted two-second epochs from the continuously recorded MEG signal for the measurements, resulting in 150 trials for the pre (baseline) and post-TMS condition, respectively. We then performed artefact rejection in two steps. First, we visually inspected trials for eye movements, muscle artefacts or channel jumps and rejected the affected trials. Furthermore, we eliminated dead and very noisy channels. Two out of 100 data sets (one from the cTBS and one from the IAF protocol) had to be excluded because of very poor data quality. In a second step, the data

sets were processed using an Independent Component Analysis (ICA; http://sccn.ucsd.edu/eeglab/) to correct for heartbeat-related artefacts. We entered 80 randomly sampled trials into the ICA in order to get independent components with a distinct time course and spatial topography. We identified those components (two in the majority of cases) that captured cardiac activity through visual inspection. Afterwards, the respective weights of the ICA were applied to the whole data set, artefact components were removed and the original data were reconstructed without the impact of the artefact. To ensure similar signal-to-noise-ratio for direct comparisons between the placebo (sham) and active TMS conditions, the trial number was adjusted to the minimum remaining trial number for the two time points (pre and post) and the compared conditions (sham and the respective active TMS protocols). To keep trial numbers in a comparable range, maximum trial number was set to 90.

Spectral power analyses derived from auditory cortex

As patients had to leave the MEG between pre and post-TMS sessions, all analyses were performed at source level in order to obtain robust effects, in contrast to a potential analysis at sensor level, which would have been more susceptible to altered head positions in the sensor helmet (from pre to post as well as over different days).

For each patient, we created a head model fitted to the head shape of the first MEG measurement using a multisphere approach (Huang et al. 1999). This yielded a grid covering the entire brain with a resolution of 1 cm and

assured that the same grid would be used in a single participant across all sessions. The leadfield for each grid point, however, was separately calculated for each session to account for potentially altered positioning of the sources with respect to the sensors.

Data were then analysed for the region of interest, defined as the auditory cortex (Brodman Area 41 & 42; Talairach atlas) ipsilateral to the TMS stimulation side. We also investigated oscillatory brain activity contralateral to the stimulation side. This analysis did not reveal any consistent effects; we thus do not describe them in further detail. In order to estimate power spectra for the region of interest, we employed a multitaper spectral estimation method (Percival, 1993) to the ICA-corrected raw data and kept the complex Fourier coefficients. We used a different smoothing for low (2-12 Hz) and high frequencies (30–90 Hz) so that the data were multiplied with a set of orthogonal Slepian tapers, yielding a frequency smoothing of +/- 1 Hz for low and +/- 5 Hz for high frequencies. We then constructed spatial filters (with fixed orientation) using the lcmv-algorithm (lcmv beamformer; Van Veen et al., 1997) for each grid point within the region of interest. This was again accomplished for low and high frequencies respectively by filtering the non-ICA corrected data in the corresponding frequency bands (2-12 Hz, 30-90 Hz). Afterwards, we projected the complex values into source space by multiplying them with the accordant spatial filters and by calculating the complex modulus of the values. We thereby obtained absolute power values for each voxel within the region of interest. By averaging the values in the region of interest we obtained one single value for each frequency. This procedure was repeated for each patient, for both time points (pre and post)

and for the five different conditions (4 active TMS protocols & sham). Finally, spectral source estimates were normalized for each patient and condition by calculating a (post-pre)/pre ratio, reflecting the modulation of oscillatory power from pre to post TMS intervention. It should be noted that we focused on frequencies of interest that were derived from previous studies on altered oscillatory power in tinnitus patients: delta (1-3 Hz; Weisz et al., 2005), theta (4-6 Hz; Llinas et al. 1999, Moazami-Goudarzi et al., 2010), alpha (8-12 Hz; Weisz et al., 2005), gamma (Ashton et al., 2007; Weisz et al., 2007; van der Loo et al., 2009) subdivided in low gamma (30-70 Hz) and high gamma (70-90 Hz). In the next step, these values were statistically tested.

Statistical analyses of the pre-post modulations

Statistical analyses were performed using R version 2.11.1 for Mac OS X (www.r.project.org). As the complex study design entailed a small sample size and we identified various 'outliers' that, after precise investigation, we did not wish to treat as real outliers, we used a bootstrap approach for the statistical analysis. The 'outliers' or extreme values were not due to poor data quality, but rather reflect strong interindividual differences in the different stimulation protocols with somehow systematic patterns (only for specific TMS protocols and in patients with very short tinnitus duration; see figure 1 in the supplemental material for comparison). Therefore, we decided not to exclude these cases and instead use robust statistics. We always compared the pre-post ratios of the active TMS conditions against sham. Thus, the sham values were subtracted from the activation values and 1000 bootstrap replicates of

the median were generated. We used the median in order to not overemphasize the extreme values. We subsequently extracted the upper and lower quantiles corresponding to a probability of 2.5% and obtained the confidence intervals (CI) for each stimulation form, respectively. We performed this procedure for both the modulation of tinnitus loudness values and the modulation of auditory oscillatory activity in the frequency bands of interest.

Signatures of auditory brain activity reducing tinnitus loudness

Apart from analyses that focused on consistent modulations of tinnitus loudness and oscillatory activity after the different TMS protocols, we wanted to identify the signatures of oscillatory brain activity that are decisive for a strong reduction or an enhancement of tinnitus loudness. Hence, we defined the most effective stimulation protocol (among active TMS conditions) in *reducing* tinnitus loudness according to the TIM scores for each patient and analysed the according modulations in oscillatory activity. We repeated this procedure for the stimulation protocols that *increased* tinnitus loudness. For the selection of the according TMS protocol we used the TIM scores as they clearly separated the different protocols, whereas the VAS scores were more ambiguous (i.e., different protocols lead to identical modulations of tinnitus loudness). Note that we obtained similar results when excluding the ambiguous cases in the VAS assignment compared to the TIM assignment.

We conducted a further bootstrap statistic (the same method as described above) for the five frequency bands of interest (delta, theta, alpha, low gamma, high gamma) and for both increasing and decreasing tinnitus

loudness protocols. We thereby defined the signatures of neuronal activity resulting in tinnitus loudness decreases/increases within the same participants.

Signatures of whole brain activity reducing tinnitus loudness

Although it was not the focus of the present study, we examined the signatures of oscillatory brain activity in non-auditory regions that are decisive for a strong decrease or increase in tinnitus loudness. We thus performed a whole brain analysis for the stimulation protocol (individually selected) that most effectively reduced or enhanced tinnitus loudness according to the TIM and analysed power modulations from pre to post-TMS in the frequency bands of interest (delta, theta, alpha, low gamma, high gamma). For this purpose, we performed Dynamic Imaging of Coherent Sources (DICS), introduced by Gross et al. (2001). This beamformer technique optimally estimates the power for a certain location while suppressing activity at all other locations. The headmodel and leadfield were taken from the prior ROI analysis. For each grid point, we constructed a spatial filter from the cross-spectral density matrix of the MEG signal (not ICA-cleaned) at the frequency of interest (delta, alpha, gamma) and the respective leadfield. Thereafter we applied the spatial filters to the Fourier-transformed ICA-cleaned data (multitaper analysis) for the frequency of interest and divided the values by an estimate of the spatially inhomogenous noise (obtained for each gridpoint on the basis of the smallest value of the covariance matrix) in order to normalise this across participants. Afterwards we interpolated the resulting activation volumes to the individual MRI of the patients and normalised them to a

template MNI brain provided by the SPM2 toolbox (http://www.fil.ion.ucl.ac.uk/spm/software/spm2). For statistical analysis, we calculated (pre-post)/post ratios for each voxel of the source solutions respectively and tested these relative values against zero by applying a voxel-wise t-statistic. To correct for multiple comparisons, we defined a minimum cluster size (minimum number of neighbouring voxels above a given threshold that are required for a significant cluster) with AlphaSim provided by the Afni Package (http://afni.nimh.nih.gov/afni/doc/manual/AlphaSim.pdf). We thereby preserved the main non-auditory regions (> 770 voxels) that were modulated by an effective tinnitus loudness-reducing or enhancing TMS stimulation in the frequency bands of interest.

Results

Individual tolerance of the TMS stimulation

None of the patients showed serious side effects of rTMS apart from transient mild to moderate discomfort due to muscle contractions, involuntary movements of the jaw and cutaneous sensations during TMS stimulation. One patient experienced a mild headache after stimulation, which disappeared without medication after several hours. Another patient reported periods of complete absence of the tinnitus lasting for several minutes after 1Hz rTMS. Three patients reported a worsening of their tinnitus after IAF stimulation lasting for several hours up to a few days.

Tinnitus loudness modulations for the different stimulation protocols compared to sham

Matched tinnitus loudness (TIM) was significantly reduced for 1-Hz rTMS (median: -.15, CI: -.04 to -.27, $p < .05$) and not modulated for the other stimulation protocols (figure 2; upper panel). The reduction of subjective tinnitus loudness (VAS) was marginally significant for the 1-Hz (median: 0, CI: -0.4 to 0, $p < .05$) and cTBS protocols (median: 0, CI: -.25 to 0, $p < .05$), whereas it turned out to be marginally enhanced for the IAF stimulation (median: .13, CI: 0 to .26, $p < .05$). ITBS did not consistently change the tinnitus loudness (see Figure 2 (lower panel) for comparison). TIM (median: .08) and VAS (median: .06) values were not significnatly modulated by sham stimulation.

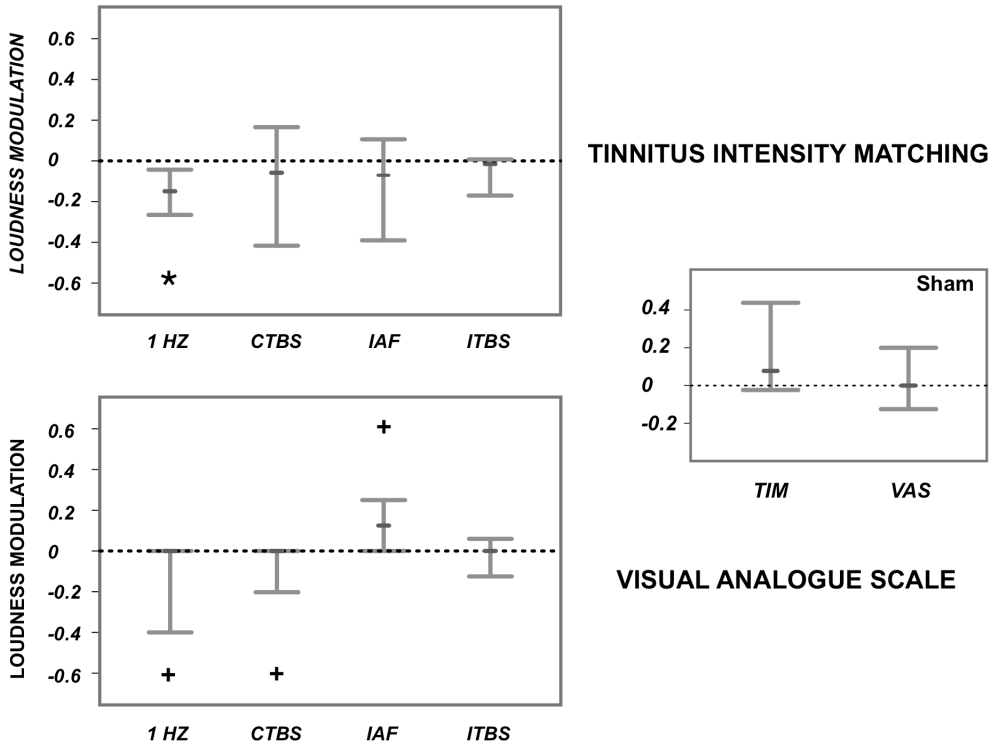


Figure 2: Consistent changes in tinnitus loudness after the four active TMS protocols (1 Hz rTMS, cTBS, IAF rTMS, iTBS) compared to sham. The upper panel displays tinnitus loudness modulations that were measured with a matched-intensity approach (TIM), while the lower panel illustrates tinnitus loudness modulations that were quantified with a visual analogue scale (VAS). Sham effects are visualised in the right panel. Shown are the 95% confidence intervals. The small bars display the median. The asterisk indicates significant modulations, while the cross points to marginally significant modulations. According to the TIM, tinnitus loudness was reduced after 1-Hz rTMS. A trend pointing to a tinnitus reduction was revealed after 1-Hz rTMS and cTBS, while tinnitus loudness was marginally enhanced after IAF rTMS.

Modulations of auditory oscillatory brain activity for the different stimulation protocols compared to sham

Auditory oscillatory activity was not consistently modulated for the delta (1-3 Hz), theta (4-6 Hz) and low gamma (30-70 Hz) frequency bands (data shown in figure 2 in the supplemental material)—that is, the confidence interval of all bootstrap statistics crossed the zero line. In contrast to this, power modulations in the alpha band were significantly reduced for the IAF stimulation (median: -.07, CI: -.54 to -.02, $p < .05$) and iTBS (median: -.10, CI: -.20 to -.004, $p < .05$), while no consistent differences were apparent in the cTBS and 1-Hz protocols (see figure 3 upper panel). Furthermore, oscillatory power in the high gamma band (70-90 Hz) was significantly reduced for 1-Hz rTMS (median: -.11, CI: -.24 to -.004, $p< .05$) and iTBS (median: -.10, CI: -.21 to -.02, $p< .05$), while no consistent differences were apparent in cTBS and IAF stimulation (figure 3, lower panel).

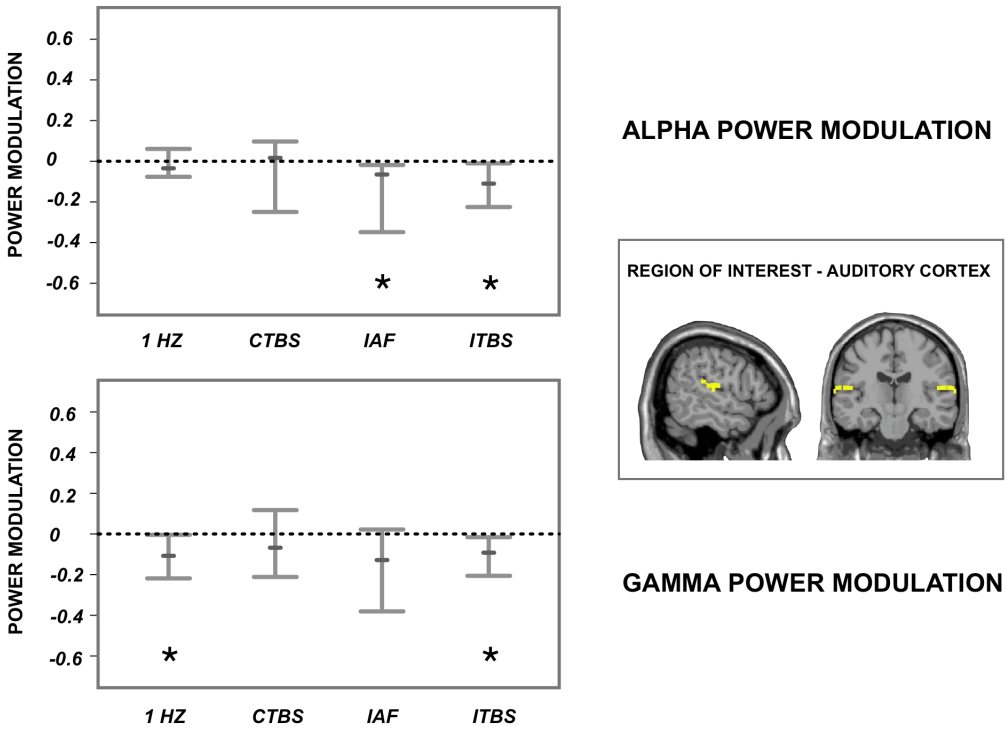


Figure 3: Consistent changes in oscillatory activity after the four active TMS protocols (1 Hz rTMS, cTBS, IAF rTMS, iTBS) compared to sham. The upper panel displays alpha power modulations, while the lower panel illustrates modulations of high gamma power at the stimulated auditory cortex. The stimulated region and region of interest are displayed on the right side. Shown are the 95% confidence intervals. The small bars display the median while the asterisks indicate that the modulations were significant. Alpha power was significantly reduced after IAF rTMS and iTBS, while gamma power was significantly decreased by 1-Hz rTMS and iTBS.

Power modulations after sham stimulation were not significant (median of alpha power: .08; median of high gamma power .06).

Signatures in auditory oscillatory power that result in strong modulations of tinnitus loudness

Selecting the stimulation protocol (only active TMS protocols were considered, not sham) that was best in reducing tinnitus loudness for each patient individually resulted in a strong tinnitus reduction from pre to post rTMS for both the subjective (VAS; median: -.27, CI: -.9 to -.14, only unambiguous cases included) and objective (TIM; median: -.13, CI: -.30 to -.03) loudness measure (both $p < .001$). Importantly, for every patient, we could identify a 'real' TMS protocol that was better at reducing tinnitus compared to the placebo sham stimulation (according to TIM scores). Loudness reductions and a distribution of the contributing stimulation protocols are shown in Figure 4.

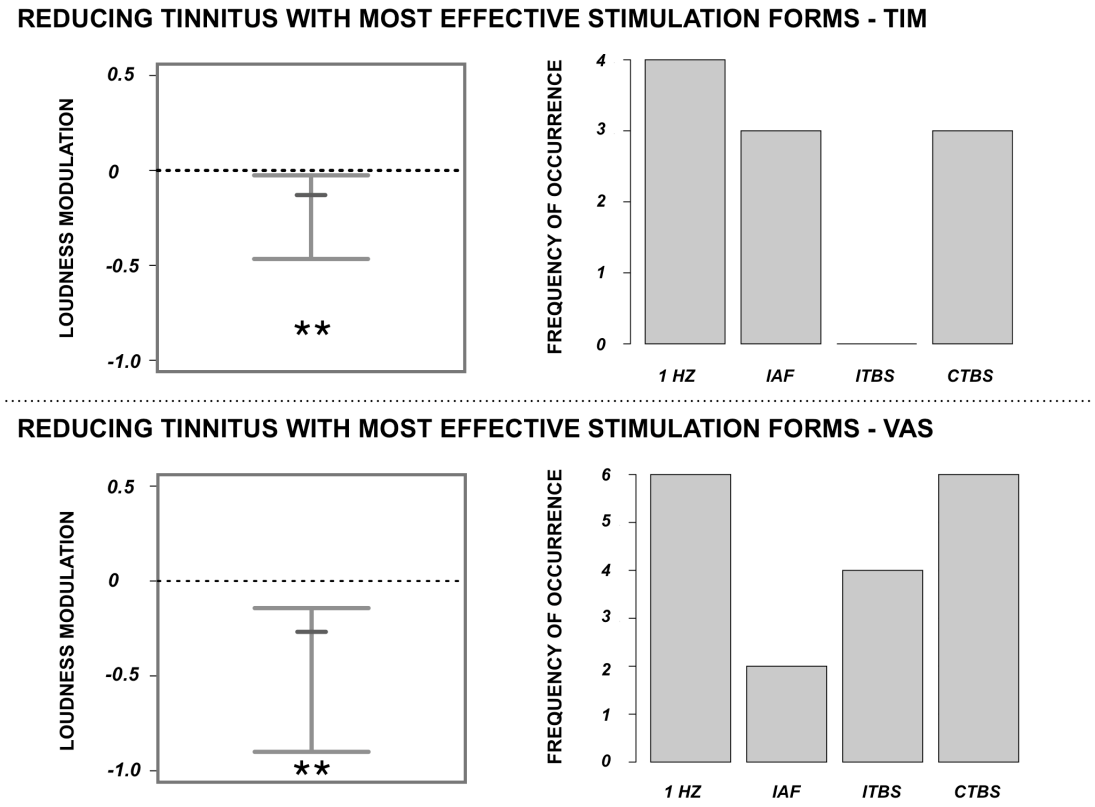


Figure 4: Changes in tinnitus loudness after application of the individually most effective stimulation protocol. The upper panel displays tinnitus loudness modulations that were measured with the tinnitus intensity matching

procedure (TIM), while the lower panel illustrates tinnitus loudness modulations that were quantified with a visual analogue scale (VAS). The 99% confidence intervals are shown on the left side. The small bars display the median. The asterisks indicate significant modulations. Tinnitus loudness was significantly reduced ($p < .001$) after application of the individually selected protocol that was best in reducing tinnitus. The distribution of these protocols is displayed on the right side. Note that, as the ambiguous cases (when selecting the most effective protocol with VAS) were included for this illustration, the summed frequency of occurrence can be higher than the total number of patients.

Analogously, we selected the stimulation protocols that consistently increased objective tinnitus loudness (TIM; median: .10, CI: .01 to .24). It should be noted that as we could not select the stimulation protocols that worsened tinnitus loudness unambiguously with the VAS scores for the majority of patients (only possible in 4 of 10 patients), we disregarded these values in further analyses. The loudness increase and a distribution of the contributing stimulation protocols are illustrated in Figure 5.

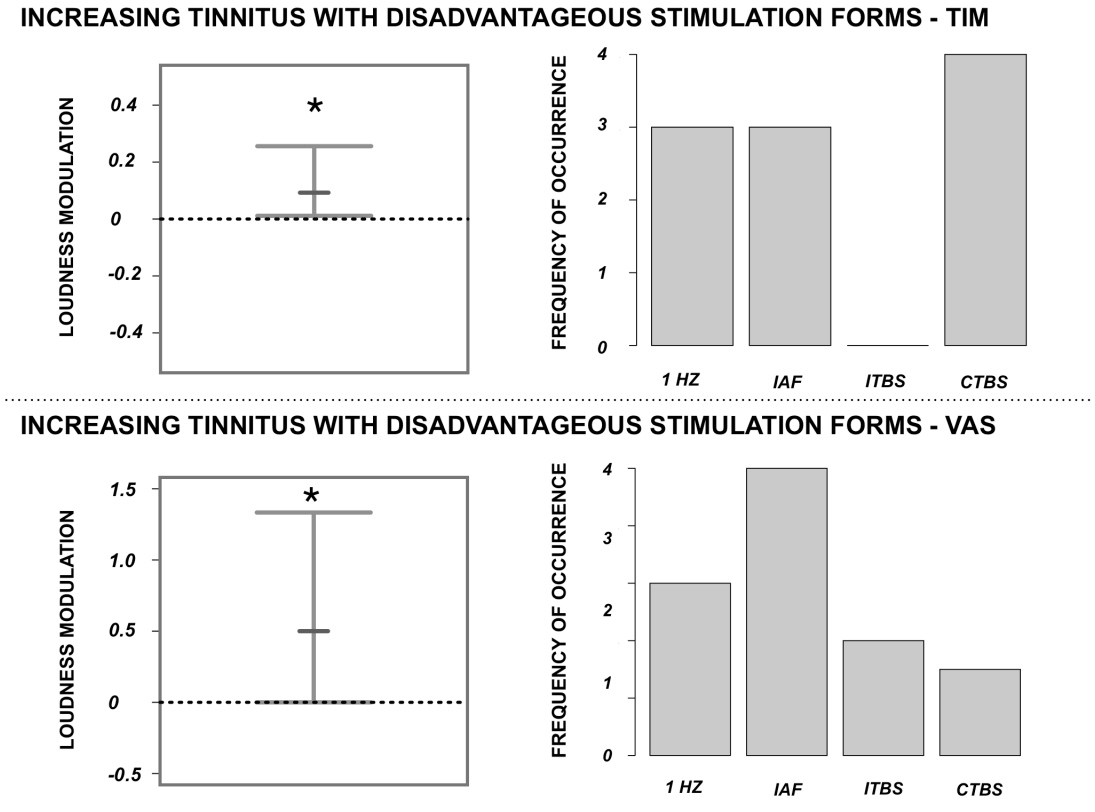


Figure 5: Changes in tinnitus loudness after application of the stimulation protocol that enhanced tinnitus loudness. The upper panel displays tinnitus loudness modulations that were measured with the tinnitus intensity matching procedure (TIM), while the lower panel illustrates tinnitus loudness modulations that were quantified using a visual analogue scale (VAS). The 95% confidence intervals are shown on the left side. The small bars display the median. The asterisks indicate significant modulations. Tinnitus loudness was significantly reduced ($p < .05$) after application of the individually selected protocol that worsened tinnitus. The distribution of these protocols is displayed on the right side. Note that, as the ambiguous cases (when selecting the most effective protocol with VAS) were included for this illustration, the summed frequency of occurrence can be higher than the total number of patients.

We could not identify any signatures of oscillatory activity in the stimulated auditory cortex related to a strong *increase* in tinnitus loudness (See figure 6). However, when looking at the modulations of oscillatory power that were associated with a strong tinnitus loudness *reduction,* it turned out that a significant power enhancement in the *alpha* band was related to the tinnitus reduction. Delta, theta and gamma (low and high) power were not consistently modulated and varied strongly. This was true for both, subjective tinnitus loudness (VAS) in the six patients that could be unambiguously assigned to one stimulation protocol as well as objective tinnitus loudness (TIM) (see Figure 6 for comparison).

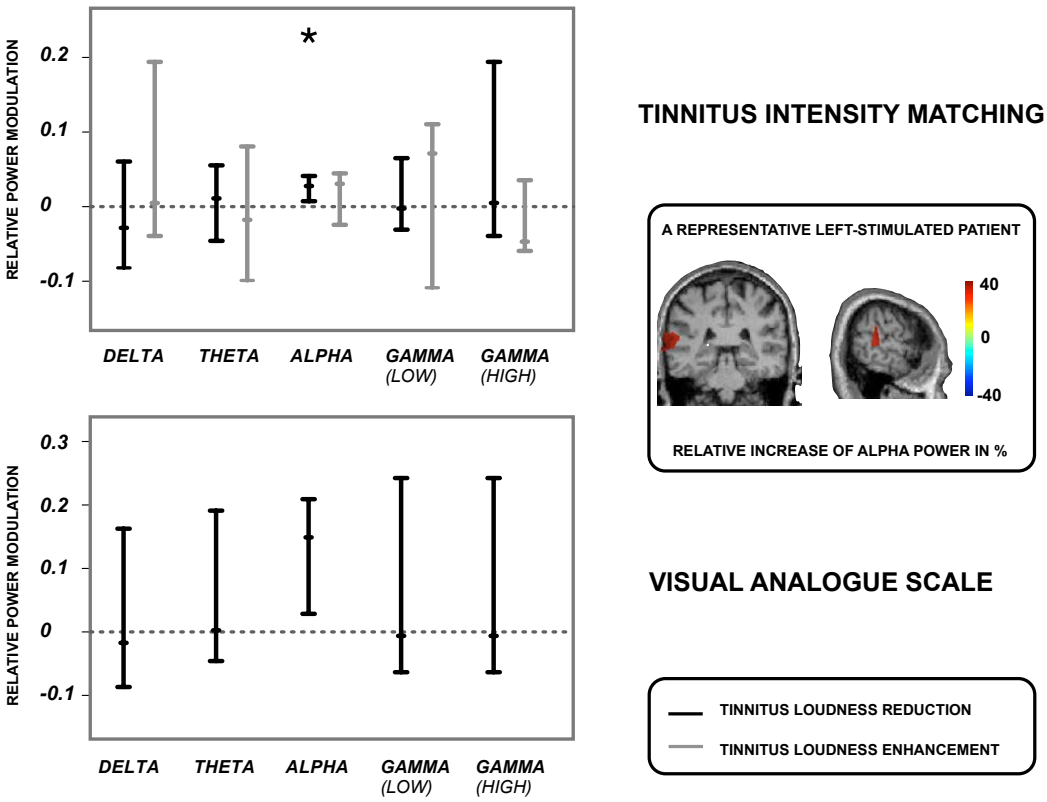


Figure 6: Changes in oscillatory activity at the stimulated auditory cortex after application of the rTMS protocols that were best in reducing (black bars) and enhancing (grey bars) tinnitus loudness. The upper panel displays power modulations that were associated with the tinnitus intensity matching procedure (TIM), while the lower panel illustrates power modulations that were related to the visual analogue scale (VAS). Displayed are the 95% confidence intervals for power modulations in the stimulated auditory cortex and the different frequency bands (delta, THETA, alpha, low gamma, high gamma). The small bars show the median, while the asterisk indicates the power modulations as significant. Note that we observed too many ambiguous cases for the VAS with respect to an increase in tinnitus loudness; we could thus not specify the according signature in oscillatory activity. Alpha power was significantly enhanced when tinnitus loudness was most effectively reduced by rTMS.

Signatures of non-auditory oscillatory power that result in a strong tinnitus loudness modulation

We did not reveal any consistent modulations of oscillatory activity associated with a strong tinnitus loudness decrease. However, we could identify left-

hemispheric dominant reductions in oscillatory activity related to an increase in tinnitus loudness. Gamma power was significantly ($p < .01$; corrected) reduced in a left prefrontal (ventromedial frontal), a left precentral and a left parieto-temporo-occipital region. Furthermore, alpha power was reduced ($p < .01$; corrected) in a left superior frontal area. The power modulations in non-auditory regions related to a tinnitus worsening are displayed in Figure 7.

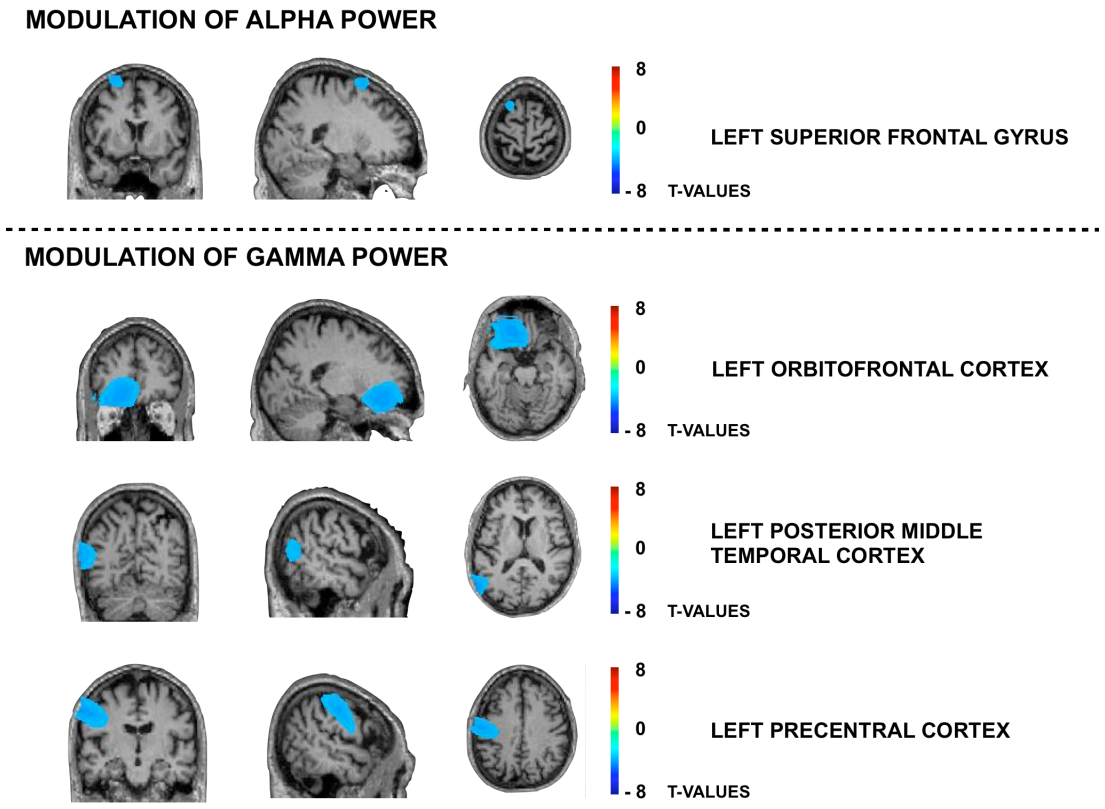


Figure 7: Changes in oscillatory activity in non-auditory brain areas after application of the rTMS protocols that were most effective in enhancing tinnitus loudness. The upper panel displays brain regions with power modulations in the alpha band, while the lower panel illustrates the areas exhibiting modulations in gamma power. Displayed are comparisons from pre to post rTMS and are quantified in t-values. Gamma power was significantly ($p < .01$; corrected) reduced in a left prefrontal, a left precentral and a left parieto-temporo-occipital region. Alpha power was reduced ($p < .01$; corrected) in a left superior frontal area.

Discussion

In the current study, we show how oscillatory brain activity is modulated in tinnitus patients by the application of four different TMS protocols (compared to sham) that are currently explored for treatment. We first focused on short-term modulations of oscillatory activity and tinnitus loudness that were consistent across patients for the specific TMS protocols, though overall effects were relatively small and varied strongly across patients. In a second step we identified the most effective stimulation protocols in decreasing (and increasing) tinnitus loudness and looked at associated modulations of oscillatory activity in auditory and non-auditory brain regions.

Consistent modulations of tinnitus loudness

We demonstrate that 1-Hz rTMS most consistently reduced tinnitus loudness (measured with a subjective and objective measure) compared to sham. However, the effects were relatively small and varied across subjects. This is in line with current literature on rTMS in tinnitus treatment that reports an impact of repeated 1-Hz rTMS sessions at the auditory cortex, albeit with moderate effect sizes and great interindividual variability (Kleinjung et al., 2007; Kleinjung et al., 2008; Plewnia, 2010). Regarding the subjective estimates of tinnitus loudness, we additionally observed an overall reduction in tinnitus loudness after cTBS and, furthermore, an increase in tinnitus loudness after IAF rTMS. Again results were only moderate and varied strongly across patients. Our finding of tinnitus relief after cTBS is consistent with the few reports on this relatively new stimulation paradigm tested for the

treatment of tinnitus (Poreisz et al., 2009; Soekadar et al., 2009). At first glance, the average increase in tinnitus loudness after IAF stimulation was rather unexpected, as most studies using high-frequency rTMS demonstrated a transient reduction of the tinnitus percept in the majority of the patients (Plewnia et al., 2003; De Ridder et al., 2005; Folmer et al., 2006; Fregni et al., 2006). However, these discrepancies were likely due to differences in the experimental designs. In most studies, alterations in tinnitus loudness were assessed immediately after rTMS, whereas we assessed changes about 10-15 minutes after rTMS. Moreover, the duration of stimulation may play a role (Gamboa et al., 2010) as we measured tinnitus loudness after the application of 1000 pulses, in contrast to a maximum of 200 pulses in all previous studies on tinnitus. Consistent with the present data, that in average point to a disinhibition of the auditory cortex and increased tinnitus loudness after prolonged high-frequency rTMS, studies in the motor system show increased excitability and facilitated motor responses after such an extensive stimulation (Peinemann et al., 2004; Quartarone et al., 2005; Fitzgerald et al., 2006).

Consistent modulations of oscillatory activity

Alpha power (8–12 Hz) was significantly reduced after treatment with IAF rTMS and iTBS in the auditory cortex ipsilateral to rTMS. It has been demonstrated that a decrease in alpha power is linked to disinhibition, whereas an increase in alpha power reflects active inhibition of the underlying neuronal tissue (Foxe et al., 1998; Worden et al., 2000; Klimesch et al., 2007; Rihs et al., 2007; Weisz et al., 2007; Romei et al., 2008; Jensen and

Mazaheri, 2010). Regarding oscillatory activity in tinnitus patients, it has been shown that tinnitus patients exhibit a reduced alpha peak compared to normal controls, which is putatively linked to reduced inhibition in the auditory cortex (Weisz et al., 2005; Weisz et al., 2007). Thus, we suggest that the decrease in alpha power after rTMS is related to a disinhibition and hence an increase in excitability of the stimulated auditory cortex.

To our knowledge, the impact of high-frequency rTMS or iTBS on *auditory* cortex excitability has not yet been investigated, despite the presence of the above-mentioned studies on tinnitus. Research in the motor system usually reports an enhancement in excitability after high-frequency (in the alpha range) rTMS and iTBS (Pascual-Leone et al., 1994; Takano et al., 2004; Huang et al., 2005; Fitzgerald et al., 2006; Di Lazzaro et al., 2011). Therefore, the decrease in alpha power after rapid-rate rTMS and iTBS fits well into the literature and furthermore extends the role of high-frequency rTMS and iTBS in increasing excitability from the motor to the auditory system.

High gamma power (70 – 90 Hz) was consistently modulated after two of the four active rTMS protocols: we detected a significant reduction after 1-Hz rTMS as well as after iTBS in the stimulated auditory cortex. In contrast to the alpha rhythm, gamma oscillations are associated with higher-order functions and active sensory processing (Gray et al., 1989; Singer, 1999). It has been demonstrated that tinnitus patients exhibit enhanced auditory gamma power compared to controls (Llinás et al., 1999; Ashton et al., 2007; Weisz et al., 2007) and that auditory gamma activity is also increased during transient tinnitus after noise trauma (Ortmann et al., 2011). Furthermore, gamma power

in the auditory cortex contralateral to the tinnitus percept has been suggested to reflect the loudness of the tinnitus percept (van der Loo et al., 2009).

Several studies have investigated the impact of low-frequency rTMS (≤ 1 Hz) on neuronal and behavioural outcomes. It has been demonstrated that low-frequency rTMS decreases cortical excitability (Chen et al., 1997; Di Lazzaro et al., 2011; for an overview see Thut and Miniussi, 2009), reduces gamma activity in schizophrenic patients (Ferrarelli et al., 2008), improves inhibitory function in tinnitus patients (Kleinjung et al., 2007; Langguth et al., 2008), reduces auditory metabolic activity in tinnitus patients (Marcondes et al., 2009) and reduces tinnitus loudness when applied during repeated sessions (Kleinjung et al., 2007). This is consistent with results from the present study that demonstrate a decrease in gamma power in the stimulated area and thus a reduction in auditory cortical activity after 1-Hz rTMS.

The effects of iTBS are rather variable and inconsistent regarding different stimulation areas: iTBS has been related to an enhanced motor cortex excitability (Huang et al., 2005) and an increased gamma power in the sensory-motor cortex of rats (Benali et al., 2011), which is in opposition to our finding of reduced gamma power after iTBS. However, studies also report an increased cortical inhibition (Trippe et al., 2009; Benali et al., 2011) as well as a reduction in the auditory steady-state response after iTBS (Lorenz et al., 2010). In general, reports on the effects of iTBS on excitability of cortical regions apart from the human motor cortex are rare and suggest that the effects are not simply transferable to non-motor brain regions (Franca et al., 2006; Poreisz et al., 2008). The only study investigating the effect of iTBS on tinnitus loudness did not reveal any consistent effects (Poreisz et al., 2009).

Furthermore, a reduction in auditory gamma activity after iTBS does not necessarily point to a generally reduced excitability since we also detected a decrease in alpha power (rather pointing to increased excitability) following iTBS as described above.

All these inconsistencies in sum, we emphasize that the relationship of alpha power, gamma power and the perception of tinnitus loudness is not sufficiently understood to date and would require further research. In the following section, we attempt to further enlighten the role of a certain pattern in oscillatory activity as a prerequisite for a change of tinnitus perception.

Signatures of oscillatory activity associated with a reduction in tinnitus loudness after rTMS in auditory brain regions

Tinnitus loudness was most effectively reduced by individually selected stimulation protocols implying that different patients profited from different protocols. Importantly, for every patient, sham stimulation was worse at reducing tinnitus loudness than the best 'real' rTMS protocol. For about half of the patients 1 Hz rTMS was most successful while the other half profited from other protocols such as IAF rTMS and cTBS. Based on this we wanted to elucidate if the different rTMS protocols having in common to effectively reduce tinnitus loudness also affect ongoing auditory cortical activity in a specific way.

Our findings demonstrate that a strong reduction in tinnitus loudness was associated with an enhancement of alpha power in the stimulated auditory

cortex (ipsilateral to rTMS), while delta, theta and gamma power were not consistently modulated and varied strongly. Therefore, we suppose that an increase in alpha power in the auditory cortex is crucial for the reduction of tinnitus loudness, whereas auditory delta, theta and gamma power seem to be related to more unspecific effects. This is in line with studies that have demonstrated a normalisation in alpha power after successful tinnitus treatment using a neurofeedback approach (Weiler et al., 2002; Dohrmann et al., 2007). Importantly, the specific role of auditory *alpha* power does not contradict the results on the *average* modulations of tinnitus loudness and oscillatory activity described in the first part of the discussion where on average effective stimulation protocols (such as 1 Hz rTMS) were not associated with increases in auditory alpha power. Due to the fact that within categories patients that profit and do not profit from a specific protocol are automatically intermingled such an analysis is less sensitive in detecting tinnitus relief specific modulations than an individualised analysis. It rather focuses on modulations that are specific for the selected stimulation protocol regardless of its potential to strongly reduce tinnitus. We therefore think that the individualised analysis is more powerful to derive the features associated with a successful rTMS tinnitus treatment and underline the importance of alpha power increases in the auditory cortex as such a relevant feature to effectively reduce tinnitus.

We would like to further point out that most studies on signatures in oscillatory activity related to tinnitus include comparisons between tinnitus patients and normal hearing controls (Llinás et al., 1999; Weisz et al., 2005; Ashton et al., 2007; Weisz et al., 2007; Moazami-Goudarzi et al., 2010). The observed

differences in neuronal activity are therefore not unequivocal and could be due to many unspecific mechanisms appearing in the tinnitus patients related to emotional or cognitive processes such as attention and evaluation. It is thus of great interest to identify the specific neuronal signatures in tinnitus patients (in this case oscillatory activity) that are related to a strong decrease (or increase) in tinnitus loudness compared to the 'normal' tinnitus perception and to find out which of these signatures must be modulated in order to successfully reduce tinnitus. With respect to our data, we again emphasise the importance of an alpha power increase in the auditory cortex for an alleviation of the tinnitus percept. The association between high auditory alpha power and tinnitus relief further corroborates the role of alpha power in the active inhibition of cortical brain regions (Klimesch et al., 2007; Weisz et al., 2007; Romei et al., 2008; Jensen and Mazaheri, 2010) and extends its role in the pathophysiology of brain diseases with an excitatory-inhibitory imbalance such as tinnitus (Eggermont and Roberts, 2004; Weisz et al., 2005). As tinnitus is predominantly characterised by a hyperexcitation in auditory brain regions (Plewnia, 2010), we suggest that enhancing auditory alpha activity is most relevant for the relief of tinnitus, putatively by increasing ongoing inhibitory mechanisms.

Signatures in oscillatory activity associated with an increase in tinnitus loudness after rTMS in non-auditory brain regions

In this study we were not able to identify any extra-auditory signatures in oscillatory activity related to tinnitus loudness reduction. However, we found

that an increase in tinnitus loudness was associated with a decrease in gamma and alpha power predominantly in left frontal regions. Specifically, tinnitus loudness increases were related to reduced alpha power in the left superior middle frontal region, which is in line with findings of increased activity in middle frontal and superior frontal regions in tinnitus patients (Wunderlich et al., 2010). The increase in tinnitus was further associated with gamma power reductions in the left prefrontal, left precentral and left posterior temporal cortex pointing to a deactivation of these regions when tinnitus loudness increased. Various studies underpin the relevance of a frontoparietal network in tinnitus perception (Mirz et al., 2000; Plewnia et al., 2007; Lanting et al., 2009; Schlee et al., 2009). It has been postulated that the prefrontal cortex integrates sensory and emotional aspects of tinnitus (Jastreboff, 1990) and is part of a network associated with conscious tinnitus perception (Weisz et al., 2005; Schlee et al., 2009). Transcranial direct current stimulation (Vanneste et al., 2010) and transcranial magnetic stimulation (Kleinjung et al., 2008) of the prefrontal cortex led to a decrease in tinnitus intensity and distress. A deactivation of the left prefrontal cortex associated with reduced positive affect (Davidson et al., 2002; Kringelbach, 2005) and an increase in pain perception (Moont et al., 2011) is in line with the worsening of the tinnitus found in the present study. The precentral region has been related to the attentional control for the selection of auditory stimuli (Westerhausen et al., 2010) and parieto-temporo-occipital regions were active during verbal auditory hallucinations (Jardri et al., 2011).

However, the relevance of the observed top-down network including left frontal and centro-parietal regions for the generation of tinnitus and the

significance of reduced alpha and gamma power in the sense of activation and deactivation must be investigated through further studies. It should also be noted that the lack of effects in non-auditory regions related to tinnitus reduction may be biased by the fact that the intervention was targeted at the auditory cortex. One may speculate that changes in tinnitus loudness through interventions focussing on other brain areas may reveal different patterns of network alterations.

Future perspective and limitations

The present results have shed further light on the pathophysiology of tinnitus and will hopefully stimulate the development of more effective therapy approaches. It appears essential to determine the signatures in auditory and non-auditory brain regions that are associated with the tinnitus percept in order to better understand this complex disease and to be able to develop more effective treatments. In this study we focused on the relationship of tinnitus loudness changes and changes in oscillatory activity in the stimulated auditory cortex and in other cortical regions. Our study confirmed that a reduction in tinnitus loudness is possible using conventional rTMS approaches; however, in line with most other studies, the general relief of the tinnitus percept was small and varied strongly across patients (Langguth et al., 2008). Considering the small sample size in the current study, we nevertheless showed that the effectiveness of rTMS in treating tinnitus could be increased significantly from 7% loudness reduction with the 'best' conventional TMS protocol (1-Hz rTMS) to 13% reduction of objective tinnitus loudness with an individually optimized stimulation. *Reductions* in the tinnitus

sensation were associated with increases in alpha power in the stimulated auditory cortex, meaning that the intervention had specific effects. The identification of alpha power increases in the stimulated area as the relevant mechanisms of action of rTMS is of high relevance as it provides an initial orientation for an individualized treatment approach. Future clinical studies may aim at identifying the optimal rTMS protocol for increasing alpha activity in the temporal cortex in the individual patient in order to enhance clinical efficacy. On the other hand, *increases* in the tinnitus sensation were related to alteration in a left-lateralised fronto-centro-parietal network, confirming the relevance of this network for tinnitus perception. Increase in tinnitus loudness may thus either result from propagated rTMS effects on non-auditory (mostly left frontal) brain regions or may be unspecific. More comprehensive clinical trials are needed in order to further explore the observed effects of temporal rTMS on cortical oscillations in tinnitus patients, regarding in addition to this clinical relevance and the persistence of these effects.

Study 3: You can't stop the music – reduced auditory alpha power and enhanced auditory-parahippocampal coupling facilitate the illusion of continuity during noise

Introduction

When we listen to a well-known song on the radio and perceive the song as continuous regardless of interruptions in the radio reception, our brain automatically fills in the missing information. The brain's capacity to generate a continuous percept even in cases of fragmentary sensory information is one of its most adaptive features. Psychoacoustic research has repeatedly shown the brain's ability to restore occluded information in the auditory modality. Such experiments have demonstrated that participants perceive acoustic information to be continuous, even if parts are completely masked by noise (Kluender et al. 1992, Leaver et al. 2009, Warren et al. 1970, Warren et al. 1972). The construction of an auditory percept involves the completion of missing auditory information and can consequently be regarded as an adaptive auditory illusion. Consistent with the view of a persisting auditory experience during illusory perception, several neuroimaging and lesion studies have disclosed neuronal activation patterns during auditory imagery or illusions that resembled those during auditory perception in nonhumans (Milner et al. 2001, Petkov et al. 2003, Petkov et al. 2007, Sugita et al. 1997) as well as humans (brain damage: Farah et al. 1988, Zatorre et al. 1993; auditory imagery in healthy controls: Halpern et al. 2001, Halpern & Zatorre 1999, Kraemer et al. 2005, Yoo et al. 2001, Riecke et al. 2011, Zatorre et al. 1996; for review see: Kosslyn et al. 2001, Hubbard et al. 2010). Petkov and

colleagues (2007) studied response patterns of auditory cortex neurons in awake macaque monkeys and found that the neuronal response patterns were identical for the perception of continuous tones and tones that included noise fractions. Lesion, fMRI and PET studies suggest an activation of (mostly the secondary) auditory cortex during imagery, a perhaps related phenomenon, of simple (Yoo et al. 2001) and more complex auditory stimuli such as speech sounds (Heinrich et al. 2008, Shahin et al. 2009) or music (Halpern et al. 1999, Kraemer et al. 2005, Zatorre et al. 1993, Zatorre et al. 1996). Importantly, the overwhelming majority of studies into auditory illusions emphasize that similar regions are activated during auditory perception and illusions. Electrophysiological studies have focused on a comparison of evoked potentials representing illusory versus non-illusory auditory percepts (Herholz et al. 2009, Micheley et al. 2003, Navarro et al. 2010, Schürmann et al. 2002, Sivonen et al. 2006) and, in line with neuroimaging studies, have revealed joint components for auditory perception and illusions.

While increasing evidence postulates that conscious perception requires specific brain states that systematically relate to specific patterns of oscillatory activity (Buzsáki 2006, Capotosto et al. 2009, Klimesch et al. 2007, Schröder et al. 2007, Thut et al. 2006), the relationship between auditory continuity illusions and oscillatory activity remains mostly unexplained. Specific oscillatory patterns that are marked by local modulations of synchronous oscillatory activity and synchronized activity between brain areas can modulate the excitability of specific regions (Klimesch et al. 2005) and open or close the windows for communication with more distant brain regions (Buzsáki & Draguhn 2004, Womelsdorf et al. 2007). The investigation of specific

oscillatory patterns thus bears the potential for gaining a deeper insight into the mechanisms underlying auditory continuity illusions. Riecke and colleagues (2009) investigated *evoked* oscillatory theta activity related to immediate auditory restoration processes and found a general increase in theta activity for interrupted tones that was weakened when the tones were incorrectly perceived as continuous. This restoration-related suppression reached its peak at about 170 ms after gap onset, was most significant between 3 and 4 Hz and was located in the right auditory cortex. The authors interpret this delta/theta suppression as reduced encoding in the right auditory cortex, resulting in an attenuation of gap perception. However, such short interruptions are likely to elicit strong evoked potentials that could explain the low frequency effect and that must be distinguished from modulations of genuine oscillatory activity. Nevertheless, in spite of this study's findings, there is a lack of research attempts to address auditory continuity illusions in terms of oscillatory activity.

According to recent literature, synchronous oscillatory activity in the alpha band (8–12 Hz) has a special role in modulating the local excitability of brain regions and significantly impacts perception (Klimesch et al. 2007, Jensen et al. 2010, Weisz et al. 2011). It has been shown in the visual system that the perception of a near-threshold stimulus depends on alpha activity in low-level visual cortical areas (Hanslmayr et al. 2007, Romei et al. 2010). For instance, Romei and colleagues (2008) could demonstrate that occipital alpha-band power correlates with the threshold for eliciting illusory visual percepts (phosphenes) by Transcranial Magnetic Stimulation. If ongoing oscillatory alpha activity has the potential to define whether near-threshold stimuli are

perceived or not, we suggest that oscillatory alpha activity could also be crucial for generating and maintaining the auditory continuity illusion. Supporting this view, the link between *auditory* alpha power (also termed *tau*: 6–12 Hz, Lethelä et al. 1997) and auditory cortical activity has also been recently established (review: Weisz et al. 2011). We thus hypothesize that auditory illusory percepts depend on auditory alpha-like activity that facilitates or inhibits auditory cortical activity and in this regard opens or closes the windows for the formation of illusory percepts. This notion is further corroborated by research on pathological auditory illusions such as tinnitus, which suggests that reduced alpha power is related to an increased phantom sound sensation (Weisz et al. 2007).

Despite local alpha power modulations in the auditory cortex, we further assume that auditory illusions are associated with synchronized activity between the auditory cortex and memory-related brain regions. This notion is derived from theoretical considerations that assume that the illusion's content is stored in memory as well as electrophysiological research suggesting that different neuronal assemblies communicate via phase synchronization of oscillatory activity (Buzsáki & Draguhn 2004, Canolty et al. 2010, Fries et al. 2005, Singer et al. 1999, Schoffelen et al. 2005, Varela et al. 2001, Womelsdorf et al. 2007). In line with this notion, several studies have reported that medial temporal lobe structures communicate with other cortex structures during encoding and retrieval of percepts through synchronization in the theta frequency band (Buzsáki et al. 2004, Jensen et al. 2005, Lega et al. 2011, Sauseng et al. 2008). The significance of memory structures in the generation of auditory illusions is further supported by research with schizophrenic

patients, which has revealed the role of memory-related medial temporal lobe structures in auditory hallucinations (Diederen et al. 2010, Jardri et al. 2011, Silberzweig et al. 1995).

In order to clarify how the human brain generates a consistent auditory percept based on fragmentary auditory information in daily life, we investigated the illusion of continuity during noise sections embedded in rock and pop music. Oscillatory brain activity was noninvasively assessed in healthy participants using magnetoencepohalography (MEG) and complemented by intracranially recorded data (ECoG) by means of subdural grid electrodes in epilepsy patients monitored during presurgical diagnostics. Based on the fact that the perception of continuity is facilitated by experience, we hypothesized that participants perceive the songs during noise as more continuous when noise sections are embedded in familiar in comparison to unfamiliar songs. We further hypothesized that the perception of continuity depends on altered oscillatory alpha activity in the auditory cortex and the synchronization of neuronal activity between the auditory cortex and medial temporal areas, presumably in the theta band.

Methods

Participants

17 right-handed volunteers reporting normal hearing and normal or corrected-to-normal sight participated in the current study (8 m/9 f, mean age 23.9). Participants were recruited via flyers posted at the University of

Konstanz and were paid following the experiment. The Ethical Committee of the University of Konstanz approved the experimental procedure and all participants gave their written informed consent prior to taking part in the study. Two participants had to be excluded due to an excessive amount of artefacts.

We additionally collected intracranial data from 6 epilepsy patients (4f/2m, mean age 24.3) at the Swiss Epilepsy Centre (EPI, Zurich). All patients underwent invasive presurgical evaluations for possible surgical treatment of their pharmacoresistant epilepsies. Experimental recordings began when a sufficient number of seizures had been recorded, antiepileptic drugs had been reintroduced and patients were waiting for the explantation of intracranial electrodes (and epilepsy surgery when possible). All reported normal hearing and normal or corrected-to-normal vision and had read and signed an informed consent form before participation. This part of the study was in compliance with the declaration of Helsinki, too, and approved by the local medical ethics committee. One patient had to be excluded because an insufficient amount of songs was rated as familiar.

Experimental Procedure

Participants were introduced to the lab facilities and informed about the experimental procedure, which consisted of three main phases (familiarity rating, data recording, continuity rating). We subsequently collected familiarity scores for 80 randomly selected songs (derived from a pool of 200 rock and pop songs) in order to later categorize the songs

according to their familiarity. Participants listened to the first ten seconds of the selected songs and were then asked to rate each song according to a visual analogue scale ranging from 1 to 5 (1 = ‘not familiar, 5 = ‘very familiar’). We could thus identify the ten most familiar and the ten most unfamiliar songs for each participant. In a second step, we replaced parts of the 20 identified songs with two seconds sections of pink noise (20 2 sec sections per song, randomly embedded in each song between 10 and 110 sec after song onset and with a minimum distance of 2 sec between sections) using Matlab (The MathWorks, Natick, MA, Version 7.5.0 R 2007b). After the participants and songs had been prepared for the MEG recording, the main experiment began. Here, participants passively listened to the 20 modified songs while their brain activity was recorded with MEG. After the MEG recording, participants were asked again to rate the songs presented in the MEG, but this time with a focus on the perception of continuity during noise. This estimate was conducted based on the first three noise sections of each song and using a visual analogue scale (“did you perceive the song throughout the noise?“, 1 = “not at all”, 5 = ”very well”). The separation of the presentation and the rating phases assured that the yielded MEG effects were not influenced by any task (participants were unaware of the fact that a rating phase would follow the MEG experiment). The familiarity rating, the presentation of the songs during MEG recording and the continuity rating were controlled using Psyscope X (Cohen et al. 1993), an open-source environment for the design and control of behavioural experiments (http://psy.ck.sissa.it/) and R version 2.11.1 for Mac OS X (www.r.project.org). The procedure of the experiment is illustrated in Figure 1.

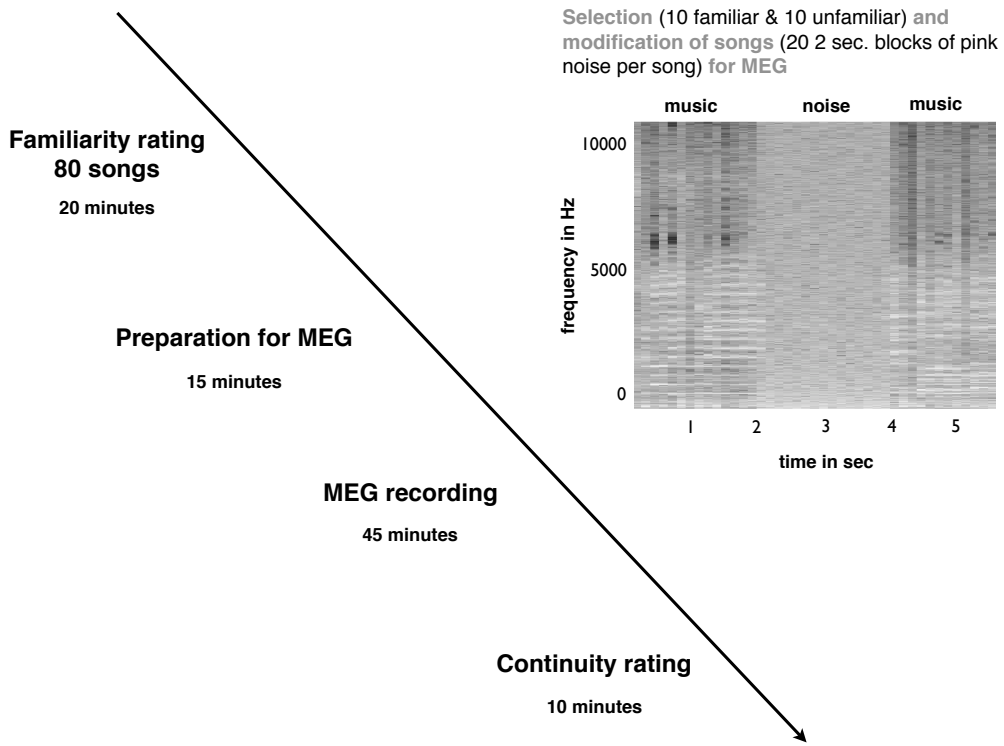


Figure 1: Illustration of the experimental procedure. The right upper panel shows the frequency spectrum of an exemplary noise section.

The experimental procedure in the Swiss Epilepsy Centre was kept as similar as possible to the MEG recordings. Nevertheless, considering the patients' condition after surgery, we decided to shorten the experiment. Familiarity ratings were based on a pool of 40 songs, from which the five most familiar and five most unfamiliar were chosen. We additionally abandoned the post rating.

MEG Data Acquisition

The MEG recordings were carried out using a 148-channel whole-head magnetometer system (MAGNESTM 2500 WH, 4D Neuroimaging, San

Diego, USA) installed in a magnetically shielded chamber (Vakuumschmelze Hanau). Prior to the recordings, individual head shapes were collected using a digitizer. Participants lay in a comfortable supine position and were asked to keep their eyes open and to focus on a fixed point on the ceiling. They were instructed to hold still and to avoid eye blinks and movements as best as possible. A video camera installed inside the MEG chamber allowed the investigator to monitor participants throughout the experiment. MEG signals were recorded with a sampling rate of 2034.51 Hz and a hardwired high-pass filter of 0.1 Hz. The audio streams were presented through a tube system with a length of 6.1 m and a diameter of 4 mm (Etymotic Research, ER30).

Intracranial Data Acquisition

Intracranial data was derived from subdural strip and grid electrodes positioned directly on the lateral surface of the brain and recorded using a DC amplifier (Refa8-31e, Advanced Neuro Technology (ANT), Enschede, The Netherlands) and the "Advanced-Source-Analysis" (ASA, Version 4.5). Subdural electrodes had stainless steel contacts with a diameter of 2.2 mm embedded in Silastic. Interelectrode spacing in strip and grid electrodes was 1 cm. Recordings were made with reference to a ground positioned as far as possible from the electrodes of interest. The sampling-rate was 256 Hz. Electrodes were implanted at different sites on the patients' brains. Data were thus obtained from a total of 140 recording sites distributed across the temporal cortex (right: 16 recording sites, left: 31 recording sites), the basal

temporal cortex (right: 16 recording sites, left: 15 recording sites) and the motor cortex (right: 31 recording sites, left: 31 recording sites). The anatomic locations of the implanted subdural grids and electrode contacts were determined in native stereotactic space by means of coregistered pre- and postoperative magnetic resonance images of 1×1×1 mm voxel resolution using the automated visualization method of Kovalev and colleagues (2005). Using the individual anatomical MRI, the electrode coordinates could then be transferred into a common MNI space also used for MEG source localization. Audio streams were presented via headphones connected to the stimulation computer. For the main experiment, patients were instructed to keep their eyes open while passively listening to the auditory stimuli.

Data Analysis

Preprocessing

We analyzed the data sets using Matlab (The MathWorks, Natick, MA, Version 7.5.0 R 2007b) and the Fieldtrip toolbox (Oostenveld et al., 2011). From the raw continuous data, we extracted epochs of four seconds lasting from one-second pre-noise-onset to one second post-noise-offset separately for the two conditions. This resulted in 200 trials (100 trials for ECoG data) for noise within familiar and 200 trials for noise within unfamiliar music. We visually inspected trials for eye movements, muscle artefacts or channel jumps and rejected the affected trials. After this procedure, no trials remained with field changes larger than 3 pT. We furthermore eliminated dead and very noisy channels. To ensure a similar

signal-to-noise-ratio across conditions, the trial numbers were equalized for the compared conditions (familiar vs. unfamiliar) by random omission.

Spectral Power Analyses (MEG)

Time-frequency distributions of the noise sections within familiar and unfamiliar music were compared at the sensor and source level. We first downsampled data to 500 Hz and then subtracted the evoked (i.e., phase-locked) response averaged over all trials (in a single subject) from each individual trial, as we were interested in induced activity not strictly phase-locked to distinct physical stimulus properties. Following this, we estimated task-related changes in oscillatory power using a multitaper FFT time-frequency transformation (Percival 1993) with frequency-dependent Hanning tapers (time window: $\Delta t=4/f$ sliding in 50 ms steps). We calculated power for 3 to 30 Hz in steps of 1 Hz and tested the obtained time-frequency power distribution for the noise periods within the familiar versus unfamiliar musical contexts using a pointwise dependent samples T-statistic. Based on the resulting time-frequency statistic we could define time and frequency bands of interest for source localization.

As a next step, Dynamic Imaging of Coherent Sources (DICS) – a frequency-domain adaptive spatial filtering algorithm (Gross 2001) – was performed to identify the sources of the time-frequency effects. We calculated spatial filters for a three-dimensional grid covering the entire brain volume (resolution: 1 cm) as well as the leadfields for each grid point for individual participants using a multisphere headmodel (Huang et al. 1999). We

constructed a spatial filter for each grid point from the cross-spectral density matrix of the MEG signal at the frequency and time window of interest (6.5 Hz ± 1.5 Hz, 400–1400 ms after noise onset; as obtained from sensor analysis) and the respective leadfield. We then applied the spatial filters to the Fourier-transformed data (multitaper analysis, hanning window) and normalized the resulting activation volumes to a template MNI brain provided by the SPM2 toolbox (http://www.fil.ion.ucl.ac.uk/spm/software/spm2). Finally, we compared the source solutions for familiar versus unfamiliar music using a voxel-wise T-statistic and could thereby quantify the difference in source power for identical noise periods within varying musical contexts. To correct for multiple comparisons, we defined a minimum cluster size (minimum number of neighbouring voxels above a given threshold that are required for a significant cluster) with AlphaSim from the Afni Package (http://afni.nimh.nih.gov/afni/doc/manual/AlphaSim.pdf). We were thereby able to preserve the main regions that differentiated between familiar and unfamiliar context music (> 770 voxels).

We further estimated the time-frequency representation of a selected voxel, defined as the voxel with maximal power modulation in the right auditory cortex (MNI coordinates: 56 1 –1), for both conditions (familiar and unfamiliar). This was done in order to obtain the modulated frequency band and time variation for this specific location and to facilitate a comparison of the MEG and ECoG data. We first transferred the raw and downsampled data sets into source space by multiplying them with the accordant spatial filters. Spatial filters were constructed from the covariance matrix of the averaged single trials at sensor level (latency: 0–2 sec post noise onset, 3–30 Hz) and

the respective leadfield by a Linearly-Constrained Minimum Variance (LCMV) beamformer (Van Veen). Afterwards, we calculated spectral power for the voxel of interest from 3 to 30 Hz in steps of 1 Hz using a multitaper FFT time-frequency transformation (Percival 1993) with frequency-dependent Hanning tapers (time window: $\Delta t=4/f$ sliding in 50 ms steps). The obtained time-frequency power distribution for the representative right auditory voxel was then compared using a pixel-wise dependent samples T-statistic. We thus preserved the frequency and time periods that were significantly modulated at a 'virtual electrode' in the right auditory cortex for noise sections within familiar compared to unfamiliar music.

Spectral Power Analyses (ECoG)

In analogy to the MEG data analyses, we calculated time-frequency distributions of the noise sections within familiar as well as unfamiliar music for the intracranial data sets. After subtracting the evoked response averaged over all trials from each individual trial we estimated task-related changes in oscillatory power using a multitaper FFT time-frequency transformation (Percival 1993) with frequency dependent Hanning tapers (equal parameters as above). We calculated power for 3 to 30 Hz in steps of 1 Hz and tested the resulting time-frequency power distribution for the noise periods within familiar and unfamiliar context music using a within-subject cluster-based permutation test (Maris and Oostenveld 2007). We considered a cluster p-value of 5% (two-tailed testing) as significant. We could thereby extract the significant time-frequency modulations and electrodes related to a differential processing

of noise sections within familiar and unfamiliar context music for each patient.

Phase Synchrony Analyses (ECoG)

As we hypothesized that memory-related regions would be additionally involved in the generation of the auditory illusion, we investigated whether basal temporal electrodes (close to the hippocampus and parahippocampal region) would phase synchronize with auditory cortex electrodes and could thus be functionally connected to the auditory cortex during the illusion-elicited alpha power modulations (Lachaux et al. 1999). This analysis was achieved in one representative patient with a grid consisting of right temporal and additional basal temporal electrodes. A right basal temporal electrode exhibiting a strong theta power increase during noise within familiar music was selected as the electrode of interest for phase synchrony analysis (MNI coordinates: 48 -28 -25, in the vicinity of the parahippocampal gyrus). As an auditory reference we selected an electrode belonging to a previously disclosed negative alpha cluster and located in the vicinity of the MEG alpha reduction (MNI coordinates: 61 -2 -13). To note, the Euclidian distance between the selected intracranial electrode and the virtual MEG electrode (voxel with maximal alpha power modulation in MEG analysis as described above) was 1.32 cm and thus very small when considering a MEG grid resolution of 1 cm. For the quantification of phase synchrony between the basal temporal and right temporal electrodes we estimated the cross-spectral density matrix using a multitaper FFT time-frequency transformation (Percival 1993) with frequency dependent Hanning tapers (equal parameters as for

spectral power analyses). In this way we obtained cross spectra between the two signals for each time and frequency point. From these cross-spectra we could then estimate the phase locking values by estimating the consistency of phase differences between the two signals across trials. If the phase differences between two oscillators deviate from uniformity they are likely to communicate with each other, whereas uniform distribution of phase differences indicate the independence of two oscillators (Lachaux et al. 1999). The statistical significance of the phase locking values was established using a bootstrap statistic. We therefore compared the phase locking values for noise sections within familiar music to the ones related to unfamiliar music. Thus, the values in condition 1 were subtracted from the values in condition 2 and 500 bootstrap replicates of the difference were generated. We subsequently extracted the upper and lower quantiles corresponding to a probability of 2.5% and disregarded all phase locking values outside of the confidence interval.

Phase Synchrony Analyses (MEG)

In order to further compare the ECoG findings with the MEG data, we wanted to identify potentially memory-related brain regions that are functionally connected to the auditory cortex during the illusion-elicited alpha power modulations based on the MEG data. As our beamformer power analyses did not reveal specific medial temporal areas exhibiting theta power enhancement that could have served as regions of interest, we calculated phase synchrony between a right auditory reference voxel (voxel with maximal power

modulation, as obtained from source alpha power analysis; MNI coordinates: 56 1 –1) and all other voxels in the brain. The frequency of interest for phase synchrony was set to 5 Hz according to the results of the ECoG phase synchrony analysis. We first Fourier-transformed the sensor data (multitaper analysis, hanning window, latency: 0–2 s after noise onset, frequency 5 Hz) and extracted the complex values containing phase information. We then transferred these complex values into source space by multiplying them with the according spatial filters. Spatial filters were constructed from the covariance matrix of the averaged single trials at sensor level (latency: 0–2 sec post noise onset, 3–30 Hz) and the respective leadfield by a Linearly-Constrained Minimum Variance (LCMV) beamformer. We converted these complex values into angles (radians) and calculated the difference between the reference voxel and all other voxels for each trial. This refers to the above mentioned 'phase difference' between voxels (Lachaux et al. 1999). Using these values we then calculated the circular mean over all trials and employed a Fisher-Z transformation in order to assure normal distribution across participants. We thereby received phase locking values for each voxel and the two conditions. Finally, we compared the phase synchrony source representations between familiar and unfamiliar music using a voxel-wise T-statistic. We obtained as a result of this the relative phase locking values for each voxel, which quantify the average change of connectivity between conditions. We again defined a minimum cluster size of 770 voxels as significant according to AlphaSim (http://afni.nimh.nih.gov/afni/doc/manual/AlphaSim.pdf), thus preserving the main regions that were differentially phase locked to the auditory cortex when

processing noise within familiar compared to unfamiliar music.

Results

Behavioural Results

As hypothesized, the illusion of continuity was significantly stronger during noise periods embedded in familiar music than in noise within unfamiliar music ($p < .001$; Figure 2).

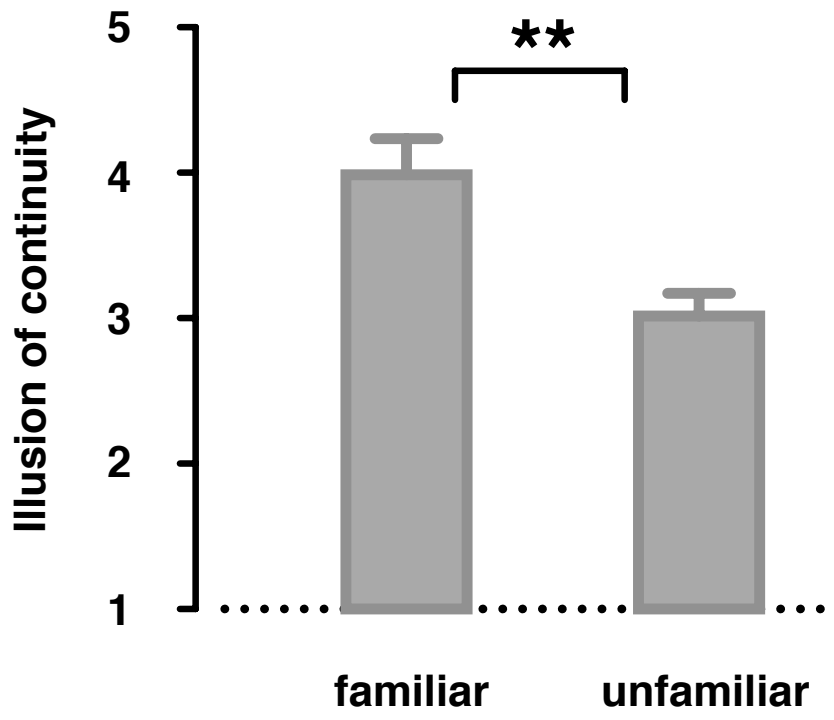


Figure 2: Behavioural data. Shown are mean values of the illusion of continuity throughout noise for familiar and unfamiliar context music across participants. The illusion of continuity was significantly stronger for noise within familiar compared to unfamiliar music.

Differences in Spectral Power for Noise within Familiar versus Unfamiliar Music – Sensor Analysis

Time-frequency analyses of the noise periods showed significant alpha power decreases during noise within familiar music compared to noise within unfamiliar music ($p<.01$). The alpha reductions in the right temporal sensors were most prominent from 5 to 8 Hz and from 400 to 1400 ms after noise onset. Despite the alpha power modulation in the right temporal sensors, we further observed an alpha power reduction in frontal sensors. In regards to the power modulation before the noise sections we noticed a power decrease in the alpha band, thus indicating a differential processing of familiar and unfamiliar songs in the auditory cortex already present when listening to the unaffected sections of music. However, as auditory stimulation obviously varied beyond the noise periods since different songs were played, observed differences could have been confounded by unequal physical properties of the selected songs. An illustration of the power modulation for familiar versus unfamiliar music is displayed in Figure 3.

Oscillatory power during noise dependent on the familiarity of the context music

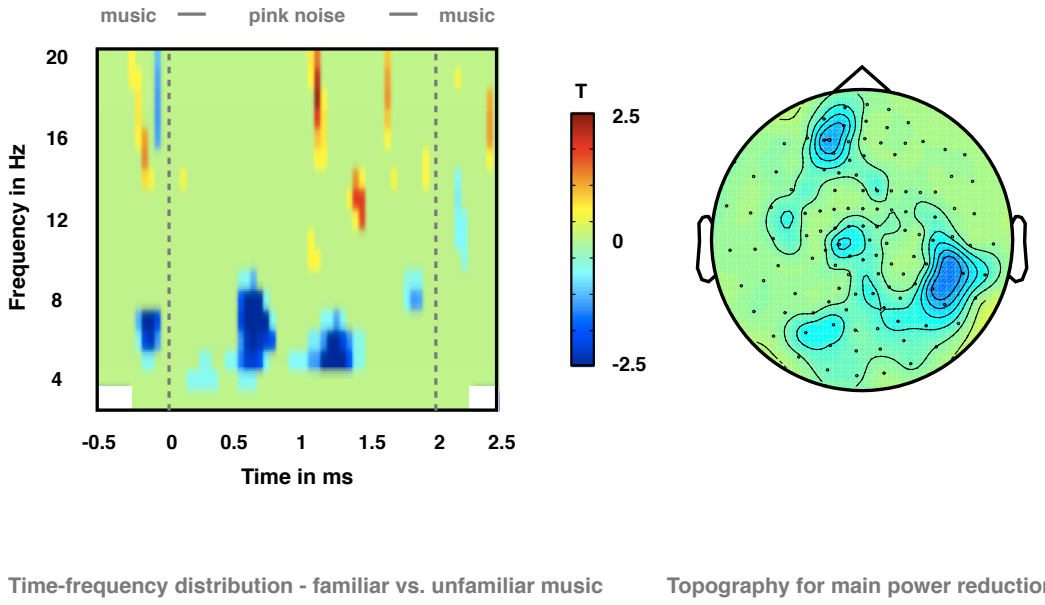


Figure 3: Oscillatory power during noise dependent on the familiarity of the context music – sensor distribution. The left panel shows the time-frequency representation of noise sections within familiar compared to unfamiliar music averaged across four representative right temporal sensors. Alpha power was significantly reduced for 5 to 8 Hz and from 400 to 1400 ms post noise onset (with short interruptions) during familiar compared to unfamiliar music. The right panel displays the topography of the significant time-frequency range. The alpha power modulations are expressed in t-values and masked with a p-value < .01. Interestingly, alpha power was already decreased before noise onset, thus indicating a differential processing of familiar and unfamiliar songs already present when listening to the unaffected sections of music.

Source Representation of Alpha Power Reductions (MEG and ECoG results)

The main MEG alpha power decreases were located in the right secondary auditory cortex (Brodmann Area 22), the right-middle frontal cortex (Brodmann Area 6) and the right inferior frontal gyrus (Brodmann Area 45). Complementing the MEG results, ECoG data point to alpha power reductions (cluster alpha < .05) in the right primary auditory cortex (Patient 2, Brodmann

Area 42), the right secondary auditory cortex (Patient 2, Brodmann Area 21 & 22) and the right middle frontal cortex (Patient 4, Brodmann Area 6). We moreover found alpha power reductions in basal temporal electrodes (Patient 5, right anterior and posterior basal temporal and left anterior basal temporal).

The time-frequency results from a representative right auditory intracranial electrode (MNI coordinates: 61 –2 –13, shown in Figure 4) indicate power decreases for familiar compared to unfamiliar noise periods, predominantly between 5 and 16 Hz and in spite of short interruptions throughout the whole noise period. Consistent with this, MEG time-frequency results obtained from a representative right temporal 'virtual electrode' (voxel with the strongest auditory alpha power reduction, MNI coordinates: 56 1 –1) again suggest a decrease in alpha power when noise is embedded in familiar music when compared to unfamiliar music. The alpha power decrease was strongest between 7 and 16 Hz (compared to 5-8 Hz regarding sensor analysis) and expanded throughout the whole noise period. An illustration of the MEG and ECoG effects is given in Figure 4.

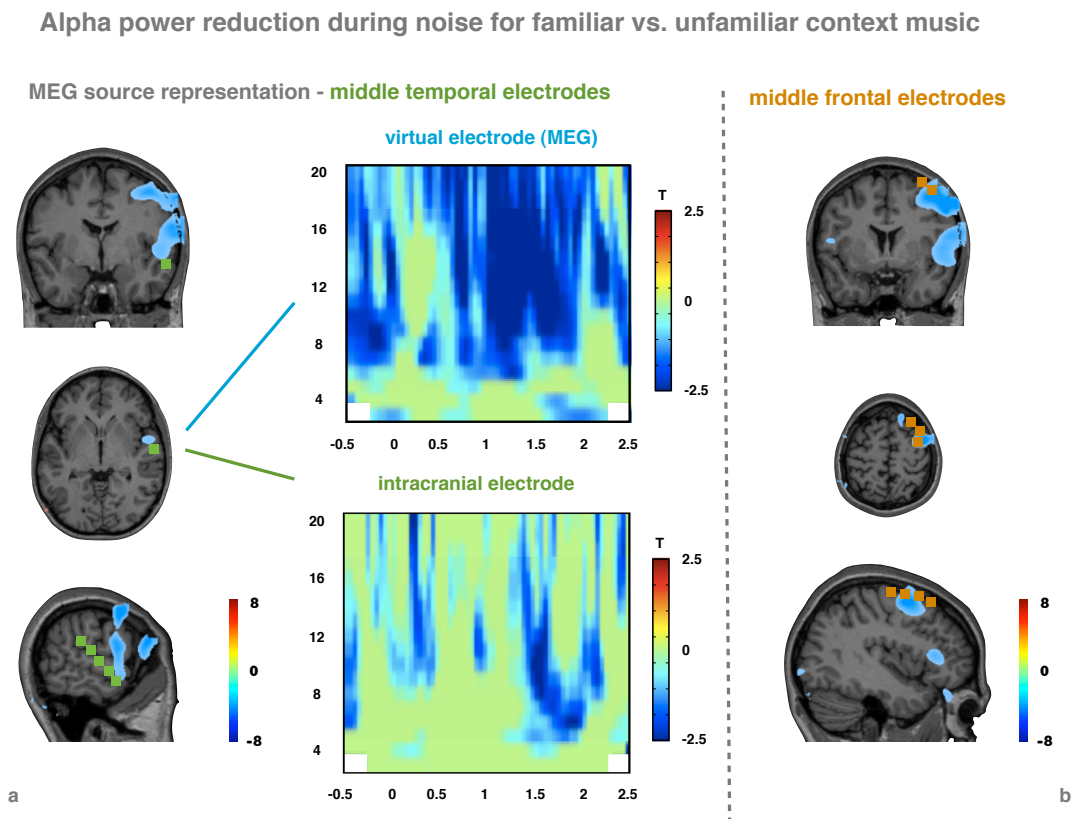


Figure 4: Alpha power reduction during noise dependent on the familiarity of the context music – MEG source localisation and ECoG data. Panel *a* (left side) shows the localisation of the alpha power decrease (derived from sensor analysis) in the brain. MEG alpha power modulations are expressed in t-values (familiar compared to unfamiliar musical context) and masked with a p-value <. 05. The green squares display intracranial electrodes that showed significant alpha power reductions, again for noise periods within familiar compared to unfamiliar music. Both, MEG an ECoG data point to significant alpha power reductions for noise within familiar compared to unfamiliar music in the right auditory cortex. The right upper side of panel *a* displays the time-frequency distribution at a right temporal virtual electrode (MEG data), while the right lower side shows the time-frequency distribution at a representative intracranial right temporal electrode. The spectral power modulations are again expressed in t-values and masked with a p-value < .05. The ECoG and MEG virtual electrode analysis both indicate power decreases for familiar compared to unfamiliar noise periods, predominantly between 6 and 16 Hz and in spite of short interruptions throughout the whole noise period. Panel *b* shows significant alpha power reductions for noise within familiar compared to unfamiliar music in the right middle frontal cortex. MEG alpha power modulations are again expressed in t-values and masked with a p-value <. 05. The orange squares display intracranial electrodes that showed significant alpha power reductions in the right middle frontal cortex.

A complete list of intracranial electrodes that were parts of significant clusters is included in the supplemental material. Despite these clusters, with activity changes occurring predominantly in the alpha band, we could not elucidate any significant temporal or basal temporal cluster with power modulations peaking in lower-frequency bands such as theta (4-6 Hz). However, we observed a prominent power increase at a single right (MNI coordinates: 48 -28 -25, shown in Figure 5) and left basal temporal electrode (Patient 2, close to parahippocampal formation) peaking at 4 Hz and becoming most dominant in the second part of the noise period. Such a theta power increase (4 Hz) in the basal temporal electrodes could point to memory-related processes relevant for the maintenance of the auditory continuity illusion. We therefore regarded these electrodes as basal temporal electrodes of interest for the subsequent phase synchrony analysis, even though they were not part of a significant cluster.

Phase Synchrony of the Right Auditory Cortex with the Parahippocampal Formation (MEG and ECoG results)

In order to investigate communication between the right auditory cortex and memory-related medial temporal structures during the processing of familiar in comparison to unfamiliar noise periods, we performed a phase synchrony analysis. As our first step, we examined phase synchrony in a patient with implanted right temporal and basal temporal electrodes. Phase synchrony between the selected right temporal (MNI coordinates: 61 –2 –13) and right parahippocampal electrodes (MNI coordinates: 48 –28 –25) of interest (see

section on power results) was significantly enhanced (bootstrap statistic, p<.05). The effect was strongest and most sustained at 5 Hz. Interestingly, when comparing the timing of maximal phase synchrony to maximal theta power increase, it appears that auditory–parahippocampal phase coupling preceded the theta power enhancement in the parahippocampal formation.

In a second step, we calculated the 5 Hz phase synchrony of a right auditory reference voxel with the rest of the brain for the MEG data. In line with the ECoG results, we could disclose the right parahippocampal cortex as the main region exhibiting significantly enhanced phase synchrony with the right auditory cortex during the processing of familiar compared to unfamiliar noise periods (p<.01). See figure 5 for comparison.

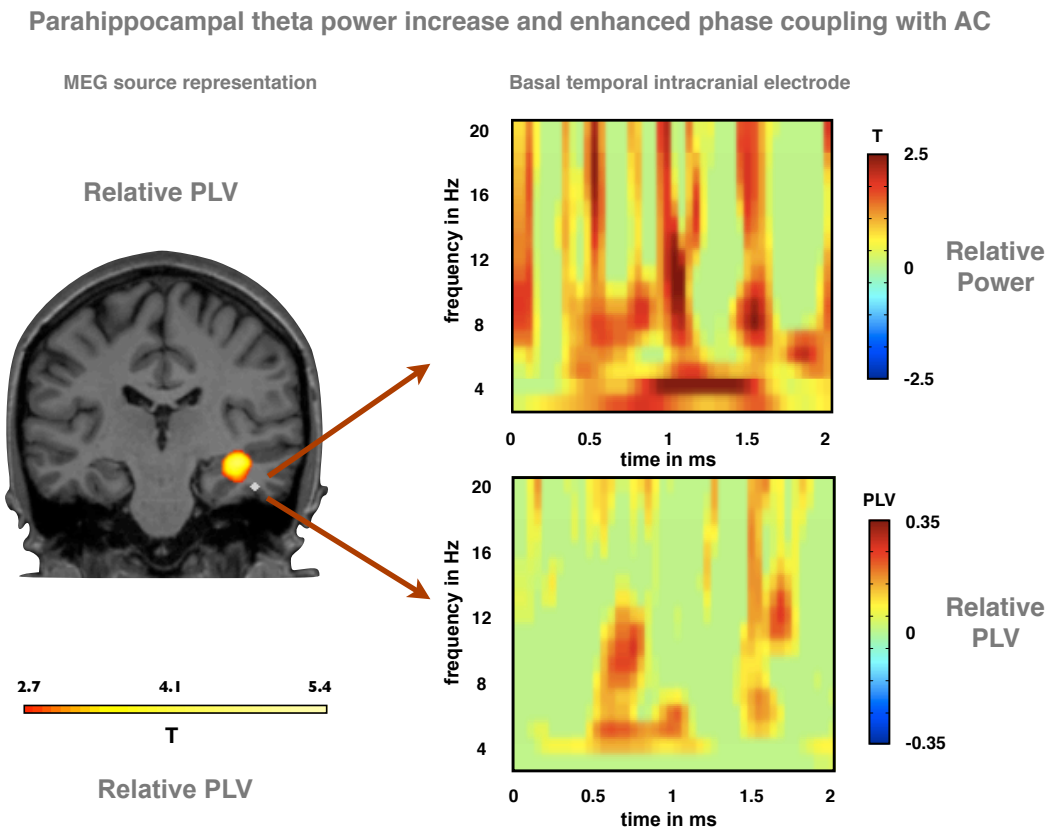


Figure 5: Parahippocampal theta power increase and enhanced phase coupling with the right auditory cortex. The left panel displays the region that

showed a significant change of phase locking with a representative right auditory voxel during processing of noise in the context of familiar compared to unfamiliar music. Phase synchrony with the right auditory cortex was significantly increased for the right parahippocampal formation. Increases are expressed in t-values and masked with a p-value < .05. The white square shows a representative intracranial electrode in the right parahippocampal formation. The time-frequency distribution of this intracranial electrode is shown in the right upper panel. Modulations are expressed in t-values and masked with a p-value < .01. Theta power is significantly enhanced during processing of noise within familiar compared to unfamiliar musical context at the right parahippocampal intracranial electrode. The right lower panel shows the spectral distribution of phase synchrony modulations for noise within familiar compared to unfamiliar music between the representative right parahippocampal intracranial electrode and a representative right temporal electrode shown in figure 4 (both electrodes were in the same patient). The Modulation of phase synchrony is again expressed in t-values and masked with a p-value < .01. Phase synchrony between the right auditory cortex and the right parahippocampal formation is increased during noise within familiar musical context, as corroborated by the MEG and representative ECoG data sets.

Discussion

In the current study, we demonstrate how oscillatory activity is modulated during the generation and, importantly, in the maintenance of an auditory illusion. The behavioral data confirm that a differential perception of identical noise periods was elicited merely by manipulating the familiarity of the context music: participants reported having significantly stronger perception of the music during pink noise when this noise was embedded in familiar music than when this occurred in unfamiliar music.

Two main neural processes were associated with this illusory percept of music continuation: first, auditory alpha power was reduced during the auditory music illusion, and second, the right auditory cortex exhibiting this strong alpha suppression was concomitantly synchronized with the right parahippocampal formation, likely involved in filling in missing sensory

information from memory. In the following discussion, we evaluate the potential role of the auditory as well as non-auditory alpha power decrease against the body of extant literature and, in a second step, scrutinize the involvement of memory-related regions in the maintenance of the illusion of continuity.

Alpha Power Decrease in the Auditory Cortex

According to MEG sensor analysis, auditory oscillatory activity was reduced between 5 and 8 Hz in the frequency range of the auditory alpha rhythm (Lethelä et al. 1997, Weisz et al. 2011) during the perception of illusory music. It has been suggested that the auditory alpha rhythm emerges in slightly different frequency bands (theta to common alpha band) depending on the task or the method (Weisz et al. 2011). At sensor level, auditory alpha activity is often weakly expressed in comparison to the dominant visual as well as sensory and motor alpha rhythms. Such parallel processes as well as those unrelated to the task could therefore obstruct the comprehensive identification of relevant auditory cortical alpha processes at surface level. Regarding intracranial data, we indeed observed the auditory alpha power decrease in a slightly higher and broader frequency band (5–15 Hz) than with MEG sensor analysis; this decrease also expanded throughout the whole noise period. Interestingly, the virtual electrode analysis based on MEG data elucidated a time-frequency distribution reminiscent of the ECoG data: alpha power was reduced in a slightly higher and more widespread frequency band (6–16 Hz) and was more sustained than in the MEG sensor analysis. The ECoG data

and the virtual electrode analysis based on MEG data therefore give a corroborating picture of auditory cortical activity when maintaining the illusion.

We thus postulate that, during perception of illusory music, alpha power (5–16 Hz) is decreased in the right auditory cortex throughout the whole noise period. Interestingly, the time-frequency distributions from MEG sensor and ECoG analysis seem to be more interrupted than the MEG 'virtual electrode' analysis. This possibly points to one beneficial effect of such a virtual electrode analysis. The rather discontinuous MEG sensor effect might depend on the higher noise level at the sensors as well as the potential influence of other interfering alpha generators in the brain that are picked up by the same sensors (see above). The partly interrupted alpha power reduction revealed by ECoG analysis is probably due to the single subject analysis (in contrast to the MEG group effect).

Apart from the alpha power decrease in the right middle frontal and right inferior frontal gyrus (which is discussed in the following section), we observed the main alpha power decrease during the auditory illusion of continuing music in the right secondary auditory cortex. The corresponding intracranial electrodes support the MEG findings of decreased alpha power in the right secondary auditory cortex. Interestingly, left auditory intracranial electrodes did not show such a modulation, which is again consistent with the MEG data. Despite the exclusive activation of the secondary auditory cortex in the MEG analysis, we observed an alpha power reduction in two intracranial electrodes that were located in the vicinity of the right primary auditory cortex (BA 42), potentially pointing to an additional involvement of early auditory areas during illusory music perception. However, as the location of these

electrodes did not allow us to clearly differentiate between the primary (BA 41/42) and secondary (BA 22) auditory cortex, we confined the interpretation of our effects to the secondary auditory cortex. The involvement of the right secondary auditory cortex is consistent with fMRI studies that demonstrate an activation of this region during musical illusions (Halpern et al. 1999, Halpern et al. 2001, Hubbard et al. 2010, Leaver et al. 2009, Leaver et al. 2010, Zatorre et al. 2005, Zatorre et al. 2009). The results are also supported by research on auditory continuity illusions using complex auditory stimuli other than music, which suggests activation of mainly the secondary and not of the primary auditory cortex during auditory illusions (Bunzeck et al. 2005, Heinrich et al. 2008, Riecke et al. 2011, Schürmann et al. 2002, Shahin et al. 2009). However, this is probably due to the complex nature of the stimuli, as simpler stimuli can also elicit activation in the primary auditory cortex during illusory perception (Petkov et al. 2007). Findings in the literature are ambiguous with respect to the lateralization of musical illusions or imagery (a perhaps related phenomenon). Most research postulates a predominantly right-hemispheric activation associated with instrumental music and a left-hemispheric dominance linked to the verbal components of music (Halpern et al. 2004, Patel & Balaban 2001, Zatorre et al. 1996, Zatorre et al. 2002, Zatorre et al. 2005). Our finding of an exclusively right auditory cortex modulation during illusory music perception, however, suggests that specific aspects of the music (such as the song's melody, which is predominantly processed in the right hemisphere) are particularly relevant for the generation of a musical illusion. This has to be clarified in further studies that more specifically

address the question of hemispheric differences in auditory continuity illusions.

With the data of the present experiment we again confirm the notion that similar regions are activated during auditory illusions and auditory perception—here reflected in reduced alpha power in the secondary auditory cortex (Heinrich et al. 2008, Kraemer et al. 2005, Shahin et al. 2009, Zatorre et al. 1993, Yoo et al. 2001). We furthermore extend current EEG findings that postulate common components during auditory perception and illusions (Herholz et al. 2008, Herholz et al. 2009, Micheley et al. 2003, Navarro et al. 2010, Schürmann et al. 2002, Sivonen et al. 2006) to the notion that auditory alpha activity is modulated during the auditory illusion, similar to modulation during auditory perception (Lethelä et al. 1997, Weisz et al. 2011). The importance of auditory alpha power in perception has only recently gained in interest and its functional role remains unexplored. Nevertheless, there exists good evidence that an alpha-like rhythm is also present in the auditory system and that this rhythm is involved in modulating perception similar to the visual alpha rhythm (Weisz et al. 2011). In analogy to the visual system (Hanslmayr et al. 2007, Klimesch et al. 2007, Romei et al. 2010, Thut et al. 2006), lower auditory alpha power is associated with a higher excitability of the auditory cortex and could thus serve as basis for the illusory auditory percept throughout noise – as found in the current study. In agreement with the potential role of auditory alpha for the generation of illusory percepts, tinnitus research shows that patients who chronically perceive an illusory sound exhibit significantly less auditory alpha power. A potential explanation forwarded by Weisz and colleagues (2005) is that high alpha power serves to

inhibit auditory cortical neurons from spontaneously synchronizing as well as producing illusory percepts and that this excitatory-inhibitory balance is chronically out of control in tinnitus patients. Counteracting the overexcitation of the auditory cortex by, for instance, rTMS indeed reduces tinnitus (Langguth et al. 2008) and diminishes more complex auditory hallucinations (Cosentino et al. 2010). We thus conclude that increased auditory cortex excitability, reflected in the current experiment in reduced alpha power, probably provides the basis for perceiving an auditory illusion in healthy participants. Despite this disinhibition of the auditory cortex and the concomitant increased probability that an illusory percept is elicited, low alpha power could facilitate the communication with more distant brain regions (Buzsáki&Draguhn 2004, Womelsdorf et al. 2007). Such a communication between the excited auditory cortex and memory-related regions could be the crucial component for closing perceptual gaps during noise and enabling a continuous music perception. The potential interaction of the auditory cortex with memory-related regions is discussed in the final section.

Alpha Power Reduction in Non-Auditory Regions

Although it was not the focus of the current experiment, we also disclosed a significant non-auditory alpha power decrease in the right middle frontal/precentral cortex and the right inferior frontal cortex. The power reduction in the right middle frontal cortex was further substantiated by ECoG data, while we had no intracranial electrodes implanted in the inferior frontal cortex. It is well established that the right precentral cortex is activated during imagery of verbal and non-verbal music alike (Halpern & Zatorre 1999,

Halpern et al. 2001, Leaver et al. 2009, Rao et al. 1997, Zatorre et al. 1996) as it could support the generation of an auditory image when one sings (verbal) or, for instance, hums (nonverbal) to oneself (Hubbard et al. 2010, Halpern & Zatorre 1999). The second non-auditory structure with significantly less alpha power during the musical illusion was the inferior frontal cortex. FMRI studies investigating the cerebral substrates of musical imagery confirm an activation of this region during musical imagery or illusions (Griffiths et al. 2000, Leaver et al. 2009, Schön et al. 2010). The inferior frontal cortex may be involved in the processing and integration of musical information over time and in the comparison of previously stored music sequences with current auditory stimulation (Janata et al. 2002, Tillmann et al. 2003, Tillmann et al. 2006, Watanabe et al. 2008). Results of the present study and results from the literature thus suggest that non-auditory regions are also relevant for the maintenance and generation of musical illusions. The actual percept of illusory music, however, is likely to depend on activity in the auditory cortex itself. As hypothesized above, we suggest that local alpha power in the auditory cortex increases the probability of perceiving an illusory percept and that communication with more distant brain regions could support the generation and maintenance of this illusory percept. This aspect is further highlighted in the next section.

Phase Synchrony of the Auditory Cortex with the Parahippocampal Region

As mentioned above, we suggest that, in addition to increased auditory cortex excitability, the illusion of continuing music likely depends on communication with memory-related regions where additional information related to the songs

is stored. ECoG data indeed indicate a theta power increase at basal temporal intracranial electrodes (close to the parahippocampal formation) while we could not disclose such a power increase using MEG source analysis. An increase in theta power in memory-related structures, as disclosed by the ECoG data, is in line with studies on enhanced theta activity during the encoding and retrieval of working-memory items (Klimesch et al. 2001, Lega et al. 2011, Tesche & Karhu 2000, Tesche et al. 1999). The ECoG findings thus point to an activation of memory-related regions during the musical illusion. However, for a transfer of information to occur, the information stored and activated in memory (here the parahippocampal cortex) has to be exchanged with the auditory cortex. This requires the synchronization of the auditory cortex and the parahippocampal region through phase coupling (Buzsáki & Draguhn 2004, Canolty et al. 2010, Fries et al. 2005, Schoffelen et al. 2005, Singer et al. 1999, Varela et al. 2001, Womelsdorf et al. 2007) so that the two regions become synchronously excited and can communicate with each other (Buzsáki & Draguhn 2004). This process corresponds with the results of the present study, which demonstrate that the right secondary auditory cortex (associated with the actual illusory percept) and the right parahippocampal region (retrieving from long-term memory) are synchronized in the theta band during the illusory maintenance of music during noise. Such an auditory-parahippocampal synchronization during the music illusion is supported by the current ECoG and MEG data. The result is also interesting with regards to methodological issues that suggest a higher sensitivity of MEG phase-locking analyses compared to MEG power analyses for ‘deeper’ structures such as the

parahippocampal formation; the theta increase was only visible in ECoG, while phase locking was observed in both methods.

In line with the observed auditory-parahippocampal low-frequency coupling, several studies report that medial temporal lobe structures communicate with other cortex structures during encoding and retrieval of percepts through synchronization in the theta frequency band (Buzsáki et al. 2004, Fries et al. 2005, Fuentemilla 2010, Jensen et al. 2005, Lega et al. 2011, Sauseng et al. 2008). The participation of memory-related medial temporal lobe structures in the generation of auditory illusions—and in particular the parahippocampal formation—is further supported by research on auditory hallucinations in schizophrenia patients (Diederen et al., 2010, Jardri et al. 2011, Silberzweig et al. 1995). According to Munoz-Lopez (2010), anatomical pathways from the parahippocampal formation to the auditory association areas form the basis for auditory memory. This is reinforced by studies that demonstrate an association between the parahippocampal cortex and the recognition of familiar music as well as emotional aspects in music processing (Gosselin et al. 2006, Satoh et al. 2006) that are relevant for the storage of music in the episodic long-term memory (Eschrich & Altenmüller 2008). An activation of the parahippocampus also seems to be relevant for the storage of more general context information (Eichenbaum et al. 2006, Eichenbaum et al. 2007) and is, for instance, associated with auditory verbal memory (Ino et al. 2004). For the present experiment, we suggest that memory content stored in the parahippocampal cortex shapes the processing of the ambiguous auditory noise stimulus through extensive communication between the auditory and parahippocampal cortex. Owing to this communication, neuronal activity in the

highly excitable auditory cortex is shaped such that an illusion of continuing music can be generated.

Conclusion

With the present data we aimed to elucidate the neurophysiological processes that underlie the illusion of continuing music through noise interruptions. Based on our data, we suggest that two main processes are responsible for the generation of such an illusion. First, alpha power in the right auditory cortex is decreased, pointing to an increased excitability of the right auditory cortex and an increased probability of experiencing an illusory percept. Second, the parahippocampal formation that stores the memory contents associated with the illusion communicates with the highly excitable auditory cortex and thus shapes neuronal activity in the auditory cortex, thereby generating the illusion of continuing music.

References

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: 23-28.

Baguley DM, Axon P, Winter IM, Moffat DA. The effect of vestibular nerve section upon tinnitus. Clinical otolaryngology and allied sciences. 2002; 27: 219-226.

Bastiaansen MC, Böcker KB, Brunia CH, de Munck JC, Spekreijse H. Event-related desynchronization during anticipatory attention for an upcoming stimulus: a comparative EEG/MEG study. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2001; 112: 393-403.

Beck DM, Kastner S. Top-down and bottom-up mechanisms in biasing competition in the human brain. Vision research. 2009; 49: 1154-1165.

Belin P, McAdams S, Smith B et al. The functional anatomy of sound intensity discrimination. The Journal of neuroscience : the official journal of the Society for Neuroscience. 1998; 18: 6388-6394.

Benali A, Trippe J, Weiler E et al. Theta-burst transcranial magnetic stimulation alters cortical inhibition. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2011; 31: 1193-1203.

Besle J, Fischer C, Bidet-Caulet A, Lecaignard F, Bertrand O, Giard M. Visual activation and audiovisual interactions in the auditory cortex during speech perception: intracranial recordings in humans. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2008; 28: 14301-14310.

Bressler SL, Tang W, Sylvester CM, Shulman GL, Corbetta M. Top-down control of human visual cortex by frontal and parietal cortex in anticipatory visual spatial attention. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2008; 28: 10056-10061.

Broadbent DE. The role of auditory localization in attention and memory span. Journal of experimental psychology. 1954; 47: 191-196.

Bunzeck N, Wuestenberg T, Lutz K, Heinze HJ, Jäncke L. Scanning silence: mental imagery of complex sounds. NeuroImage. 2005; 26: 1119-1127.

Buschman TJ, Miller EK. Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. Science (New York, NY). 2007; 315: 1860-1862.

Buzsáki G. Rhythms of the Brain. Oxford University Press. 2006. New York.

Buzsáki G, Draguhn A. Neuronal oscillations in cortical networks. Science (New York, NY). 2004; 304: 1926-1929.

Canolty RT, Ganguly K, Kennerley SW et al.. Oscillatory phase coupling coordinates anatomically dispersed functional cell assemblies. Proceedings of the National Academy of Sciences of the United States of America. 2010; 107: 17356-17361.

Capotosto P, Babiloni C, Romani GL, Corbetta M. Frontoparietal cortex controls spatial attention through modulation of anticipatory alpha rhythms. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2009; 29: 5863-5872.

Chen R, Classen J, Gerloff C et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology. 1997; 48: 1398-1403.

Cherry EC. Some Experiments on the Recognition of Speech, with One and with Two Ears. The Journal of the Acoustical Society of America. 1953; 25

Cohen J, MacWhinney B, Flatt M, Provost J. PsyScope: An Interactive Graphical System for Designing and Controlling Experiments in the Psychology Laboratory Using Macintosh Computers. Behavior Methods, Research, Instruments, and Computers. 1993; 25: 257-271.

Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. Nature reviews Neuroscience. 2002; 3: 201-215.

Cosentino G, Giglia G, Palermo A et al. A case of post-traumatic complex auditory hallucinosis treated with rTMS. Neurocase. 2010; 16: 267-272.

Cusack R, Carlyon RP, Robertson IH. Auditory midline and spatial discrimination in patients with unilateral neglect. Cortex; a journal devoted to the study of the nervous system and behavior. 2001; 37: 706-709.

Davidson JD, Hugdahl, K. Brain Asymmetry. Cambridge Massachusetts: MIT Press; 1995;

De Ridder D, Verstraeten E, Van der Kelen K et al. Transcranial magnetic stimulation for tinnitus: influence of tinnitus duration on stimulation parameter choice and maximal tinnitus suppression. Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology. 2005; 26: 616-619.

Di Lazzaro V, Dileone M, Pilato F et al. Modulation of Motor Cortex Neuronal Networks by rTMS: Comparison of Local and Remote Effects of Six Different Protocols of Stimulation. Journal of neurophysiology. 2011; 105: 2150-2156.

Diederen KM, Neggers SF, Daalman K et al. Deactivation of the parahippocampal gyrus preceding auditory hallucinations in schizophrenia.

The American journal of psychiatry. 2010; 167: 427-435.

Dietrich V, Nieschalk M, Stoll W, Rajan R, Pantev C. Cortical reorganization in patients with high frequency cochlear hearing loss. Hearing research. 2001; 158: 95-101.

Dohrmann K, Weisz N, Schlee W, Hartmann T, Elbert T. Neurofeedback for treating tinnitus. Progress in brain research. 2007; 166: 473-485.

Dufour A, Touzalina, P, Candas, Y. Rightward shift of the auditory subjective straight ahead in right- and left-handed subjects. Neuropsychologia. 2007; 45: 447-453.

Eggermont JJ, Roberts LE. The neuroscience of tinnitus. Trends in neurosciences. 2004; 27: 676-682.

Eichenbaum H. Remembering: functional organization of the declarative memory system. Current biology : CB. 2006; 16: R643-5.

Eichenbaum H, Yonelinas AP, Ranganath C. The medial temporal lobe and recognition memory. Annual review of neuroscience. 2007; 30: 123-152.

Engel AK, Fries P, Singer W. Dynamic predictions: oscillations and synchrony in top-down processing. Nature reviews Neuroscience. 2001; 2: 704-716.

Eschrich S, Münte TF, Altenmüller EO. Unforgettable film music: the role of emotion in episodic long-term memory for music. BMC neuroscience. 2008; 9: 48.

Farah MJ, Levine DN, Calvanio R. A case study of mental imagery deficit. Brain and cognition. 1988; 8: 147-164.

Ferrarelli F, Massimini M, Peterson MJ et al. Reduced evoked gamma oscillations in the frontal cortex in schizophrenia patients: a TMS/EEG study. The American journal of psychiatry. 2008; 165: 996-1005.

Finlayson PG, Kaltenbach JA. Alterations in the spontaneous discharge patterns of single units in the dorsal cochlear nucleus following intense sound exposure. Hearing research. 2009; 256: 104-117.

Fitzgerald PB, Fountain S, Daskalakis ZJ. A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2006; 117: 2584-2596.

Folmer RL, Carroll JR, Rahim A, Shi Y, Hal Martin W. Effects of repetitive transcranial magnetic stimulation (rTMS) on chronic tinnitus. Acta oto-laryngologica Supplementum. 2006; 96-101.

Fox MD, Corbetta M, Snyder AZ, Vincent JL, Raichle ME. Spontaneous

neuronal activity distinguishes human dorsal and ventral attention systems. Proceedings of the National Academy of Sciences of the United States of America. 2006; 103: 10046-10051.

Foxe JJ, Simpson GV, Ahlfors SP. Parieto-occipital approximately 10 Hz activity reflects anticipatory state of visual attention mechanisms. NEUROREPORT. 1998; 9: 3929-3933.

Franca M, Koch G, Mochizuki H, Huang YZ, Rothwell JC. Effects of theta burst stimulation protocols on phosphene threshold. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2006; 117: 1808-1813.

Fregni F, Marcondes R, Boggio PS et al. Transient tinnitus suppression induced by repetitive transcranial magnetic stimulation and transcranial direct current stimulation. European journal of neurology : the official journal of the European Federation of Neurological Societies. 2006; 13: 996-1001.

Fries P. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends in cognitive sciences. 2005; 9: 474-480.

Fries P, Womelsdorf T, Oostenveld R, Desimone R. The effects of visual stimulation and selective visual attention on rhythmic neuronal synchronization in macaque area V4. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2008; 28: 4823-4835.

Fuentemilla L, Penny WD, Cashdollar N, Bunzeck N, Düzel E. Theta-coupled periodic replay in working memory. Current biology : CB. 2010; 20: 606-612.

Gamboa OL, Antal A, Moliadze V, Paulus W. Simply longer is not better: reversal of theta burst after-effect with prolonged stimulation. Experimental brain research Experimentelle Hirnforschung Expérimentation cérébrale. 2010; 204: 181-187.

Ghazanfar AA, Schroeder CE. Is neocortex essentially multisensory? Trends in cognitive sciences. 2006; 10: 278-285.

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: 166-172.

Gosselin N, Samson S, Adolphs R et al. Emotional responses to unpleasant music correlates with damage to the parahippocampal cortex. Brain : a journal of neurology. 2006; 129: 2585-2592.

Gray CM, König P, Engel AK, Singer W. Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. NATURE. 1989; 338: 334-337.

Gregoriou GG, Gotts SJ, Zhou H, Desimone R. High-frequency, long-range

coupling between prefrontal and visual cortex during attention. Science (New York, NY). 2009; 324: 1207-1210.

Griffiths TD. Musical hallucinosis in acquired deafness. Phenomenology and brain substrate. Brain : a journal of neurology. 2000; 123: 2065-2076.

Gross J, Kujala J, Hämäläinen M, Timmermann L, Schnitzler A, Salmelin R. Dynamic imaging of coherent sources: Studying neural interactions in the human brain. Proceedings of the National Academy of Sciences of the United States of America. 2001; 98: 694-699.

Gross J, Schmitz F, Schnitzler I et al. Modulation of long-range neural synchrony reflects temporal limitations of visual attention in humans. Proceedings of the National Academy of Sciences of the United States of America. 2004; 101: 13050-13055.

Haegens S, Händel BF, Jensen O. Top-down controlled alpha band activity in somatosensory areas determines behavioral performance in a discrimination task. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2011; 31: 5197-5204.

Hallam RS, Jakes SC, Hinchcliffe R. Cognitive variables in tinnitus annoyance. The British journal of clinical psychology / the British Psychological Society. 1988; 27: 213-222.

Halpern AR. Cerebral substrates of musical imagery. Annals of the New York Academy of Sciences. 2001; 930: 179-192.

Halpern AR, Zatorre RJ. When that tune runs through your head: a PET investigation of auditory imagery for familiar melodies. Cerebral cortex (New York, NY : 1991). 1999; 9: 697-704.

Hamidi M, Slagter HA, Tononi G, Postle BR. Repetitive Transcranial Magnetic Stimulation Affects behavior by Biasing Endogenous Cortical Oscillations. Frontiers in integrative neuroscience. 2009; 3: 14.

Hanslmayr S, Aslan A, Staudigl T, Klimesch W, Herrmann CS, Bäuml KH. Prestimulus oscillations predict visual perception performance between and within subjects. NeuroImage. 2007; 37: 1465-1473.

Heinrich A, Carlyon RP, Davis MH, Johnsrude IS. Illusory vowels resulting from perceptual continuity: a functional magnetic resonance imaging study. Journal of cognitive neuroscience. 2008; 20: 1737-1752.

Herholz SC, Lappe C, Knief A, Pantev C. Imagery mismatch negativity in musicians. Annals of the New York Academy of Sciences. 2009; 1169: 173-177.

Huang MX, Mosher JC, Leahy RM. A sensor-weighted overlapping-sphere head model and exhaustive head model comparison for MEG. Physics in

medicine and biology. 1999; 44: 423-440.

Huang MX, Mosher JC, Leahy RM. A sensor-weighted overlapping-sphere head model and exhaustive head model comparison for MEG. Physics in medicine and biology. 1999; 44: 423-440.

Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron. 2005; 45: 201-206.

Hubbard TL. Auditory imagery: empirical findings. Psychological bulletin. 2010; 136: 302-329.

Ino T, Doi T, Kimura T, Ito J, Fukuyama H. Neural substrates of the performance of an auditory verbal memory: between-subjects analysis by fMRI. Brain research bulletin. 2004; 64: 115-126.

Jacobs J, Kahana MJ, Ekstrom AD, Fried I. Brain oscillations control timing of single-neuron activity in humans. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2007; 27: 3839-3844.

Jardri R, Pouchet A, Pins D, Thomas P. Cortical activations during auditory verbal hallucinations in schizophrenia: a coordinate-based meta-analysis. The American journal of psychiatry. 2011; 168: 73-81.

Jastreboff PJ. Phantom auditory perception (tinnitus): mechanisms of generation and perception. Neuroscience research. 1990; 8: 221-254.

Jensen O. Reading the hippocampal code by theta phase-locking. Trends in cognitive sciences. 2005; 9: 551-553.

Jensen O, Mazaheri A. Shaping functional architecture by oscillatory activity: gating by inhibition. 2010; 4: 168.

Jin Y, Potkin SG, Kemp AS et al. Therapeutic effects of individualized alpha frequency transcranial magnetic stimulation (alphaTMS) on the negative symptoms of schizophrenia. Schizophrenia bulletin. 2006; 32: 556-561.

Jones SR, Kerr CE, Wan Q, Pritchett DL, Hämäläinen M, Moore CI. Cued spatial attention drives functionally relevant modulation of the mu rhythm in primary somatosensory cortex. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2010; 30: 13760-13765.

Kaltenbach JA. Summary of evidence pointing to a role of the dorsal cochlear nucleus in the etiology of tinnitus. Acta oto-laryngologica Supplementum. 2006; 20-26.

Kastner S, De Weerd P, Desimone R, Ungerleider LG. Mechanisms of directed attention in the human extrastriate cortex as revealed by functional MRI. Science (New York, NY). 1998; 282: 108-111.

Kastner S, Ungerleider LG. Mechanisms of visual attention in the human cortex. Annual review of neuroscience. 2000; 23: 315-341.

Kayser C. Phase resetting as a mechanism for supramodal attentional control. Neuron. 2009; 64: 300-302.

Kayser C, Petkov CI, Lippert M, Logothetis NK. Mechanisms for allocating auditory attention: an auditory saliency map. Current biology : CB. 2005; 15: 1943-1947.

Kayser C, Petkov CI, Logothetis NK. Visual modulation of neurons in auditory cortex. Cerebral cortex (New York, NY : 1991). 2008; 18: 1560-1574.

Kelly SP, Lalor EC, Reilly RB, Foxe JJ. Increases in alpha oscillatory power reflect an active retinotopic mechanism for distracter suppression during sustained visuospatial attention. Journal of neurophysiology. 2006; 95: 3844-3851.

Kerlin JR, Shahin AJ, Miller LM. Attentional gain control of ongoing cortical speech representations in a "cocktail party". The Journal of neuroscience : the official journal of the Society for Neuroscience. 2010; 30: 620-628.

Khedr EM, Rothwell JC, El-Atar A. One-year follow up of patients with chronic tinnitus treated with left temporoparietal rTMS. European journal of neurology : the official journal of the European Federation of Neurological Societies. 2009; 10: 1468-1331.

Kleinjung T, Eichhammer P, Landgrebe M et al. Combined temporal and prefrontal transcranial magnetic stimulation for tinnitus treatment: a pilot study. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2008; 138: 497-501.

Kleinjung T, Langguth B. Strategies for enhancement of transcranial magnetic stimulation effects in tinnitus patients. The international tinnitus journal. 2009; 15: 154-160.

Kleinjung T, Steffens T, Londero A, Langguth B. Transcranial magnetic stimulation (TMS) for treatment of chronic tinnitus: clinical effects. Progress in brain research. 2007; 166: 359-367.

Kleinjung T, Vielsmeier V, Landgrebe M, Hajak G, LANGGUTH B. Transcranial magnetic stimulation: a new diagnostic and therapeutic tool for tinnitus patients. The international tinnitus journal. 2008; 14: 112-118.

Klimesch W, Doppelmayr M, Stadler W, Pöllhuber D, Sauseng P, Röhm D. Episodic retrieval is reflected by a process specific increase in human electroencephalographic theta activity. Neuroscience letters. 2001; 302: 49-52.

Klimesch W, Doppelmayr M, Yonelinas A et al. Theta synchronization during

episodic retrieval: neural correlates of conscious awareness. Brain research Cognitive brain research. 2001; 12: 33-38.

Klimesch W, Sauseng P, Gerloff C. Enhancing cognitive performance with repetitive transcranial magnetic stimulation at human individual alpha frequency. The European journal of neuroscience. 2003; 17: 1129-1133.

Klimesch W, Sauseng P, Hanslmayr S. EEG alpha oscillations: the inhibition-timing hypothesis. Brain research reviews. 2007; 53: 63-88.

Klimesch W, Sauseng P, Hanslmayr S, Gruber W, Freunberger R. Event-related phase reorganization may explain evoked neural dynamics. Neuroscience and biobehavioral reviews. 2007; 31: 1003-1016.

Kopell N, Ermentrout GB, Whittington MA, Traub RD. Gamma rhythms and beta rhythms have different synchronization properties. Proceedings of the National Academy of Sciences of the United States of America. 2000; 97: 1867-1872.

Kosslyn SM, Ganis G, Thompson WL. Neural foundations of imagery. Nature reviews Neuroscience. 2001; 2: 635-642.

Kovalev D, Spreer J, Honegger J, Zentner J, Schulze-Bonhage A, Huppertz HJ. Rapid and fully automated visualization of subdural electrodes in the presurgical evaluation of epilepsy patients. AJNR American journal of neuroradiology. 2005; 26: 1078-1083.

Kraemer DJ, Macrae CN, Green AE, Kelley WM. Musical imagery: sound of silence activates auditory cortex. NATURE. 2005; 434: 158.

Kringelbach ML. The human orbitofrontal cortex: linking reward to hedonic experience. Nature reviews Neuroscience. 2005; 6: 691-702.

Lachaux JP, Rodriguez E, Martinerie J, Varela FJ. Measuring phase synchrony in brain signals. Human brain mapping. 1999; 8: 194-208.

Lakatos P, Karmos G, Mehta AD, Ulbert I, Schroeder CE. Entrainment of neuronal oscillations as a mechanism of attentional selection. Science (New York, NY). 2008; 320: 110-113.

Lakatos P, O'Connell MN, Barczak A, Mills A, Javitt DC, Schroeder CE. The leading sense: supramodal control of neurophysiological context by attention. Neuron. 2009; 64: 419-430.

Langguth B, Ridder D, Dornhoffer JL et al. Controversy: Does repetitive transcranial magnetic stimulation/ transcranial direct current stimulation show efficacy in treating tinnitus patients? 2008; 1: 192-205.

Langguth B, Zowe M, Landgrebe M et al. Transcranial magnetic stimulation for the treatment of tinnitus: a new coil positioning method and first results.

Brain topography. 2006; 18: 241-247.

Lanting CP, de Kleine E, van Dijk P. Neural activity underlying tinnitus generation: results from PET and fMRI. Hearing research. 2009; 255: 1-13.

Lawrence NS, Ross TJ, Hoffmann R, Garavan H, Stein EA. Multiple neuronal networks mediate sustained attention. Journal of cognitive neuroscience. 2003; 15: 1028-1038.

Leaver AM, Rauschecker JP. Cortical representation of natural complex sounds: effects of acoustic features and auditory object category. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2010; 30: 7604-7612.

Leaver AM, Van Lare J, Zielinski B, Halpern AR, Rauschecker JP. Brain activation during anticipation of sound sequences. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2009; 29: 2477-2485.

Lega BC, Jacobs J, Kahana M. Human hippocampal theta oscillations and the formation of episodic memories. Hippocampus. 2011; 10: 1-14.

Lehtelä L, Salmelin R, Hari R. Evidence for reactive magnetic 10-Hz rhythm in the human auditory cortex. Neuroscience letters. 1997; 222: 111-114.

Liang H, Bressler SL, Ding M, Truccolo WA, Nakamura R. Synchronized activity in prefrontal cortex during anticipation of visuomotor processing. NEUROREPORT. 2002; 13: 2011-2015.

Llinás RR, Ribary U, Jeanmonod D, Kronberg E, Mitra PP. Thalamocortical dysrhythmia: A neurological and neuropsychiatric syndrome characterized by magnetoencephalography. Proceedings of the National Academy of Sciences of the United States of America. 1999; 96: 15222-15227.

Londero A, Langguth B, De Ridder D, Bonfils P, Lefaucheur JP. Repetitive transcranial magnetic stimulation (rTMS): a new therapeutic approach in subjective tinnitus? Neurophysiologie clinique = Clinical neurophysiology. 2006; 36: 145-155.

Lopes da Silva F. Neural mechanisms underlying brain waves: from neural membranes to networks. Electroencephalography and clinical neurophysiology. 1991; 79: 81-93.

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: 1497-1505.

Marcondes RA, Sanchez TG, Kii MA et al. Repetitive transcranial magnetic stimulation improve tinnitus in normal hearing patients: a double-blind controlled, clinical and neuroimaging outcome study. European journal of

neurology : the official journal of the European Federation of Neurological Societies. 2009; 1468-1331.

Maris E, Oostenveld R. Nonparametric statistical testing of EEG- and MEG-data. Journal of neuroscience methods. 2007; 164: 177-190.

Mayer AR, Harrington D, Adair JC, Lee R. The neural networks underlying endogenous auditory covert orienting and reorienting. NeuroImage. 2006; 30: 938-949.

Micheyl C, Carlyon RP, Shtyrov Y, Hauk O, Dodson T, Pullvermüller F. The neurophysiological basis of the auditory continuity illusion: a mismatch negativity study. Journal of cognitive neuroscience. 2003; 15: 747-758.

Miller CT, Dibble E, Hauser MD. Amodal completion of acoustic signals by a nonhuman primate. Nature neuroscience. 2001; 4: 783-784.

Mirz F, Gjedde A, Ishizu K, Pedersen CB. Cortical networks subserving the perception of tinnitus--a PET study. Acta oto-laryngologica Supplementum. 2000; 543: 241-243.

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: 40.

Moont R, Crispel Y, Lev R, Pud D, Yarnitsky D. Temporal changes in cortical activation during conditioned pain modulation (CPM), a LORETA study. Pain. 2011; 60: 709-719.

Mühlnickel W, Elbert T, Taub E, Flor H. Reorganization of auditory cortex in tinnitus. Proceedings of the National Academy of Sciences of the United States of America. 1998; 95: 10340-10343.

Mulders WH, Robertson D. Hyperactivity in the auditory midbrain after acoustic trauma: dependence on cochlear activity. Neuroscience. 2009; 164: 733-746.

Müller N, Schlee W, Hartmann T, Lorenz I, Weisz N. Top-down modulation of the auditory steady-state response in a task-switch paradigm. Frontiers in human neuroscience. 2009; 3: 1.

Munoz-Lopez MM, Mohedano-Moriano A, Insausti R. Anatomical pathways for auditory memory in primates. Frontiers in neuroanatomy. 2010; 4: 129.

Navarro Cebrian A, Janata P. Electrophysiological correlates of accurate mental image formation in auditory perception and imagery tasks. Brain research. 2010; 1342: 39-54.

Nolte G, Müller KR. Localizing and estimating causal relations of interacting

brain rhythms. Frontiers in human neuroscience. 2010; 4: 209.

Noreña AJ, Eggermont JJ. Changes in spontaneous neural activity immediately after an acoustic trauma: implications for neural correlates of tinnitus. Hearing research. 2003; 183: 137-153.

Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia. 1971; 9: 97-113.

Oostenveld R, Fries P, Maris E, Schoffelen JM. FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Computational intelligence and neuroscience. 2011; 2011: 156869.

Ortmann M, Müller N, Schlee W, Weisz N. Rapid increases of gamma power in the auditory cortex following noise trauma in humans. The European journal of neuroscience. 2011; 33: 568-575.

Ossipov M, Dussor G, Porrecca F. Central modulation of pain. The Journal of Clinical Investigation. 2010; 120: 3779-3787.

Pascual-Leone A, Valls-Solé J, Wassermann EM, Hallett M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain : a journal of neurology. 1994; 117: 847-858.

Patel AD, Balaban E. Human pitch perception is reflected in the timing of stimulus-related cortical activity. Nature neuroscience. 2001; 4: 839-844.

Peinemann A, Reimer B, Löer C et al. Long-lasting increase in corticospinal excitability after 1800 pulses of subthreshold 5 Hz repetitive TMS to the primary motor cortex. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2004; 115: 1519-1526.

Pekkola J, Ojanen V, Autti T et al. Primary auditory cortex activation by visual speech: an fMRI study at 3 T. NEUROREPORT. 2005; 16: 125-128.

Percival DB WAT. Spectral Analysis for Physical Applications: Multitaper and Conventional Univariate Techniques. Spectral Analysis for Physical Applications: Multitaper and Conventional Univariate Techniques. Cambridge, UK: Cambridge University Press; 1993.

Petkov CI, O'Connor KN, Sutter ML. Encoding of illusory continuity in primary auditory cortex. Neuron. 2007; 54: 153-165.

Pfurtscheller G, Lopes da Silva FH. Event-related EEG/MEG synchronization and desynchronization: basic principles. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 1999; 110: 1842-1857.

Plewnia C. Brain Stimulation: New Vistas for the Exploration and Treatment of

Tinnitus. CNS neuroscience & therapeutics. 2010; 1-13.

Plewnia C, Bartels M, Gerloff C. Transient suppression of tinnitus by transcranial magnetic stimulation. Annals of neurology. 2003; 53: 263-266.

Plewnia C, Reimold M, Najib A, Reischl G, Plontke SK, Gerloff C. Moderate therapeutic efficacy of positron emission tomography-navigated repetitive transcranial magnetic stimulation for chronic tinnitus: a randomised, controlled pilot study. Journal of neurology, neurosurgery, and psychiatry. 2007; 78: 152-156.

Poreisz C, Antal A, Boros K, Brepohl N, Csifcsák G, Paulus W. Attenuation of N2 amplitude of laser-evoked potentials by theta burst stimulation of primary somatosensory cortex. Experimental brain research Experimentelle Hirnforschung Expérimentation cérébrale. 2008; 185: 611-621.

Poreisz C, Paulus W, Moser T, Lang N. Does a single session of theta-burst transcranial magnetic stimulation of inferior temporal cortex affect tinnitus perception? BMC neuroscience. 2009; 10: 54.

Posner MI, Petersen SE. The attention system of the human brain. Annual review of neuroscience. 1990; 13: 25-42.

Pridmore S, Fernandes Filho JA, Nahas Z, Liberatos C, George MS. Motor threshold in transcranial magnetic stimulation: a comparison of a neurophysiological method and a visualization of movement method. The journal of ECT. 1998; 14: 25-27.

Quartarone A, Bagnato S, Rizzo V et al. Distinct changes in cortical and spinal excitability following high-frequency repetitive TMS to the human motor cortex. Experimental brain research Experimentelle Hirnforschung Expérimentation cérébrale. 2005; 161: 114-124.

Raij T, Ahveninen J, Lin FH et al. Onset timing of cross-sensory activations and multisensory interactions in auditory and visual sensory cortices. The European journal of neuroscience. 2010; 31: 1772-1782.

Rajan R, Irvine DR. Neuronal responses across cortical field A1 in plasticity induced by peripheral auditory organ damage. Audiology & neuro-otology. 1998; 3: 123-144.

Reynolds JH, Chelazzi L, Desimone R. Competitive mechanisms subserve attention in macaque areas V2 and V4. The Journal of neuroscience : the official journal of the Society for Neuroscience. 1999; 19: 1736-1753.

Riecke L, Esposito F, Bonte M, Formisano E. Hearing illusory sounds in noise: the timing of sensory-perceptual transformations in auditory cortex. Neuron. 2009; 64: 550-561.

Riecke L, van Opstal AJ, Goebel R, Formisano E. Hearing illusory sounds in

noise: sensory-perceptual transformations in primary auditory cortex. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2007; 27: 12684-12689.

Riecke L, Walter A, Sorger B, Formisano E. Tracking vocal pitch through noise: neural correlates in nonprimary auditory cortex. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2011; 31: 1479-1488.

Rihs TA, Michel CM, Thut G. Mechanisms of selective inhibition in visual spatial attention are indexed by alpha-band EEG synchronization. The European journal of neuroscience. 2007; 25: 603-610.

Rihs TA, Michel CM, Thut G. Mechanisms of selective inhibition in visual spatial attention are indexed by alpha-band EEG synchronization. The European journal of neuroscience. 2007; 25: 603-610.

Rihs TA, Michel CM, Thut G. A bias for posterior alpha-band power suppression versus enhancement during shifting versus maintenance of spatial attention. NeuroImage. 2009; 44: 190-199.

Roberts LE, Eggermont JJ, Caspary DM, Shore SE, Melcher JR, Kaltenbach JA. Ringing ears: the neuroscience of tinnitus. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2010; 30: 14972-14979.

Romei V, Gross J, Thut G. On the role of prestimulus alpha rhythms over occipito-parietal areas in visual input regulation: correlation or causation? The Journal of neuroscience : the official journal of the Society for Neuroscience. 2010; 30: 8692-8697.

Romei V, Rihs T, Brodbeck V, Thut G. Resting electroencephalogram alpha-power over posterior sites indexes baseline visual cortex excitability. NEUROREPORT. 2008; 19: 203-208.

Salinas E, Sejnowski TJ. Correlated neuronal activity and the flow of neural information. Nature reviews Neuroscience. 2001; 2: 539-550.

Salmi J, Rinne T, Koistinen S, Salonen O, Alho K. Brain networks of bottom-up triggered and top-down controlled shifting of auditory attention. Brain research. 2009; 1286: 155-164.

Salvi RJ, Wang J, Ding D. Auditory plasticity and hyperactivity following cochlear damage. Hearing research. 2000; 147: 261-274.

Sameshima K, Baccalá LA. Using partial directed coherence to describe neuronal ensemble interactions. Journal of neuroscience methods. 1999; 94: 93-103.

Satoh M, Takeda K, Nagata K, Shimosegawa E, Kuzuhara S. Positron-emission tomography of brain regions activated by recognition of familiar

music. AJNR American journal of neuroradiology. 2006; 27: 1101-1106.

Sauseng P, Klimesch W, Freunberger R, Pecherstorfer T, Hanslmayr S, Doppelmayr M. Relevance of EEG alpha and theta oscillations during task switching. Experimental brain research Experimentelle Hirnforschung Experimentation cerebrale. 2006; 170: 295-301.

Sauseng P, Klimesch W, Gerloff C, Hummel FC. Spontaneous locally restricted EEG alpha activity determines cortical excitability in the motor cortex. Neuropsychologia. 2009; 47: 284-288.

Sauseng P, Klimesch W, Gruber WR, Birbaumer N. Cross-frequency phase synchronization: a brain mechanism of memory matching and attention. NeuroImage. 2008; 40: 308-317.

Sauseng P, Klimesch W, Stadler W et al. A shift of visual spatial attention is selectively associated with human EEG alpha activity. The European journal of neuroscience. 2005; 22: 2917-2926.

Schaefer M, Noennig N, Heinze HJ, Rotte M. Fooling your feelings: artificially induced referred sensations are linked to a modulation of the primary somatosensory cortex. NeuroImage. 2006; 29: 67-73.

Schlee W, Mueller N, Hartmann T, Keil J, Lorenz I, Weisz N. Mapping cortical hubs in tinnitus. BMC biology. 2009; 7: 80.

Schoffelen JM, Oostenveld R, Fries P. Neuronal coherence as a mechanism of effective corticospinal interaction. Science (New York, NY). 2005; 308: 111-113.

Schroeder CE, Foxe J. Multisensory contributions to low-level, 'unisensory' processing. Current opinion in neurobiology. 2005; 15: 454-458.

Schroeder CE, Lakatos P. Low-frequency neuronal oscillations as instruments of sensory selection. Trends in neurosciences. 2009; 32: 9-18.

Schürmann M, Raij T, Fujiki N, Hari R. Mind's ear in a musician: where and when in the brain. NeuroImage. 2002; 16: 434-440.

Seki S, Eggermont JJ. Changes in spontaneous firing rate and neural synchrony in cat primary auditory cortex after localized tone-induced hearing loss. Hearing research. 2003; 180: 28-38.

Serences JT, Yantis S. Selective visual attention and perceptual coherence. Trends in cognitive sciences. 2006; 10: 38-45.

Shahin AJ, Bishop CW, Miller LM. Neural mechanisms for illusory filling-in of degraded speech. NeuroImage. 2009; 44: 1133-1143.

Shargorodsky J, Curhan GC, Farwell WR. Prevalence and characteristics of

tinnitus among US adults. The American journal of medicine. 2010; 123: 711-718.

Shomstein S, Yantis S. Parietal cortex mediates voluntary control of spatial and nonspatial auditory attention. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2006; 26: 435-439.

Siegel M, Donner TH, Oostenveld R, Fries P, Engel AK. Neuronal synchronization along the dorsal visual pathway reflects the focus of spatial attention. Neuron. 2008; 60: 709-719.

Singer W. Neuronal synchrony: a versatile code for the definition of relations? Neuron. 1999; 24: 49-65, 111-25.

Slagter HA, Giesbrecht B, Kok A et al. fMRI evidence for both generalized and specialized components of attentional control. Brain research. 2007; 1177: 90-102.

Smith DT, Jackson SR, Rorden C. Repetitive transcranial magnetic stimulation over frontal eye fields disrupts visually cued auditory attention. Brain stimulation. 2009; 2: 81-87.

Snyder AC, Foxe JJ. Anticipatory attentional suppression of visual features indexed by oscillatory alpha-band power increases: a high-density electrical mapping study. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2010; 30: 4024-4032.

Soekadar SR, Arfeller C, Rilk A, Plontke SK, Plewnia C. Theta burst stimulation in the treatment of incapacitating tinnitus accompanied by severe depression. CNS spectrums. 2009; 14: 208-211.

Sosa Y, Teder-Sälejärvi WA, McCourt ME. Biases of spatial attention in vision and audition. Brain and cognition. 2010; 73: 229-235.

Sugita Y. Neuronal correlates of auditory induction in the cat cortex. NEUROREPORT. 1997; 8: 1155-1159.

Takano B, Drzezga A, Peller M et al. Short-term modulation of regional excitability and blood flow in human motor cortex following rapid-rate transcranial magnetic stimulation. NeuroImage. 2004; 23: 849-859.

Taylor PC, Nobre AC, Rushworth MF. FEF TMS affects visual cortical activity. Cerebral cortex (New York, NY : 1991). 2007; 17: 391-399.

Tervaniemi M, Hugdahl K. Lateralization of auditory-cortex functions. Brain research Brain research reviews. 2003; 43: 231-246.

Tesche CD, Karhu J. Theta oscillations index human hippocampal activation during a working memory task. Proceedings of the National Academy of Sciences of the United States of America. 2000; 97: 919-924.

Thorne JD, De Vos M, Viola FC, Debener S. Cross-modal phase reset predicts auditory task performance in humans. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2011; 31: 3853-3861.

Thut G, Miniussi C. New insights into rhythmic brain activity from TMS-EEG studies. Trends in cognitive sciences. 2009; 13: 182-189.

Thut G, Nietzel A, Brandt SA, Pascual-Leone A. Alpha-band electroencephalographic activity over occipital cortex indexes visuospatial attention bias and predicts visual target detection. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2006; 26: 9494-9502.

Tillmann B, Janata P, Bharucha JJ. Activation of the inferior frontal cortex in musical priming. Brain research Cognitive brain research. 2003; 16: 145-161.

Tillmann B, Koelsch S, Escoffier N et al. Cognitive priming in sung and instrumental music: activation of inferior frontal cortex. NeuroImage. 2006; 31: 1771-1782.

Trippe J, Mix A, Aydin-Abidin S, Funke K, Benali A. Theta burst and conventional low-frequency rTMS differentially affect GABAergic neurotransmission in the rat cortex. Experimental brain research Experimentelle Hirnforschung Expérimentation cérébrale. 2009; 118:1228 – 1232.

van der Loo E, Gais S, Congedo M et al. Tinnitus intensity dependent gamma oscillations of the contralateral auditory cortex. PLoS ONE. 2009; 4: e7396.

Van Veen BD, van Drongelen W, Yuchtman M, Suzuki A. Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. IEEE transactions on bio-medical engineering. 1997; 44: 867-880.

Vanneste S, Plazier M, Ost J, van der Loo E, van de Heyning P, De Ridder D. Bilateral dorsolateral prefrontal cortex modulation for tinnitus by transcranial direct current stimulation: a preliminary clinical study. Experimental brain research Experimentelle Hirnforschung Expérimentation cérébrale. 2010; 202: 779-785.

Varela F, Lachaux JP, Rodriguez E, Martinerie J. The brainweb: phase synchronization and large-scale integration. Nature reviews Neuroscience. 2001; 2: 229-239.

von Stein A, Chiang C, König P. Top-down processing mediated by interareal synchronization. Proceedings of the National Academy of Sciences of the United States of America. 2000; 97: 14748-14753.

Warren RM, Bashford JA, Healy EW, Brubaker BS. Auditory induction: reciprocal changes in alternating sounds. Perception & psychophysics. 1994;

55: 313-322.

Warren RM, Obusek CJ, Ackroff JM. Auditory induction: perceptual synthesis of absent sounds. Science (New York, NY). 1972; 176: 1149-1151.

Watanabe T, Yagishita S, Kikyo H. Memory of music: roles of right hippocampus and left inferior frontal gyrus. NeuroImage. 2008; 39: 483-491.

Weiler EW, Brill K, Tachiki KH, Schneider D. Neurofeedback and quantitative electroencephalography. The international tinnitus journal. 2002; 8: 87-93.

Weisz N, Dohrmann K, Elbert T. The relevance of spontaneous activity for the coding of the tinnitus sensation. Progress in brain research. 2007; 166: 61-70.

Weisz N, Hartmann T, Müller N, Lorenz I, Obleser J. Alpha rhythms in audition: cognitive and clinical perspectives. Frontiers in psychology. 2011; 2: 73.

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.

Weisz N, Müller S, Schlee W, Dohrmann K, Hartmann T, Elbert T. The neural code of auditory phantom perception. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2007; 27: 1479-1484.

Westerhausen R, Moosmann M, Alho K et al. Identification of attention and cognitive control networks in a parametric auditory fMRI study. Neuropsychologia. 2010; 48: 2075-2081.

Winkowski DE, Knudsen EI. Top-down gain control of the auditory space map by gaze control circuitry in the barn owl. NATURE. 2006; 439: 336-339.

Womelsdorf T, Schoffelen JM, Oostenveld R et al. Modulation of neuronal interactions through neuronal synchronization. Science (New York, NY). 2007; 316: 1609-1612.

Worden MS, Foxe JJ, Wang N, Simpson GV. Anticipatory biasing of visuospatial attention indexed by retinotopically specific alpha-band electroencephalography increases over occipital cortex. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2000; 20: RC63.

Wu CT, Weissman DH, Roberts KC, Woldorff MG. The neural circuitry underlying the executive control of auditory spatial attention. Brain research. 2007; 1134: 187-198.

Wunderlich AP, Schönfeldt-Lecuona C, Wolf RC, Dorn K, Bachor E, Freund W. Cortical activation during a pitch discrimination task in tinnitus patients and controls--an fMRI study. Audiology & neuro-otology. 2010; 15: 137-148.

Yoo SS, Lee CU, Choi BG. Human brain mapping of auditory imagery: event-related functional MRI study. NEUROREPORT. 2001; 12: 3045-3049.

Zacharek MA, Kaltenbach JA, Mathog TA, Zhang J. Effects of cochlear ablation on noise induced hyperactivity in the hamster dorsal cochlear nucleus: implications for the origin of noise induced tinnitus. Hearing research. 2002; 172: 137-143.

Zatorre RJ, Belin P. Spectral and temporal processing in human auditory cortex. Cerebral cortex (New York, NY : 1991). 2001; 11: 946-953.

Zatorre RJ, Halpern AR. Effect of unilateral temporal-lobe excision on perception and imagery of songs. Neuropsychologia. 1993; 31: 221-232.
Zatorre RJ, Halpern AR. Mental concerts: musical imagery and auditory cortex. Neuron. 2005; 47: 9-12.

Zatorre RJ, Halpern AR, Perry DW, Meyer E, Evans AC. Hearing in the Mind's Ear: A PET Investigation of Musical Imagery and Perception. Journal of cognitive neuroscience. 1996; 8: 29-46.

Figures

Supplemental Material

Study 1:

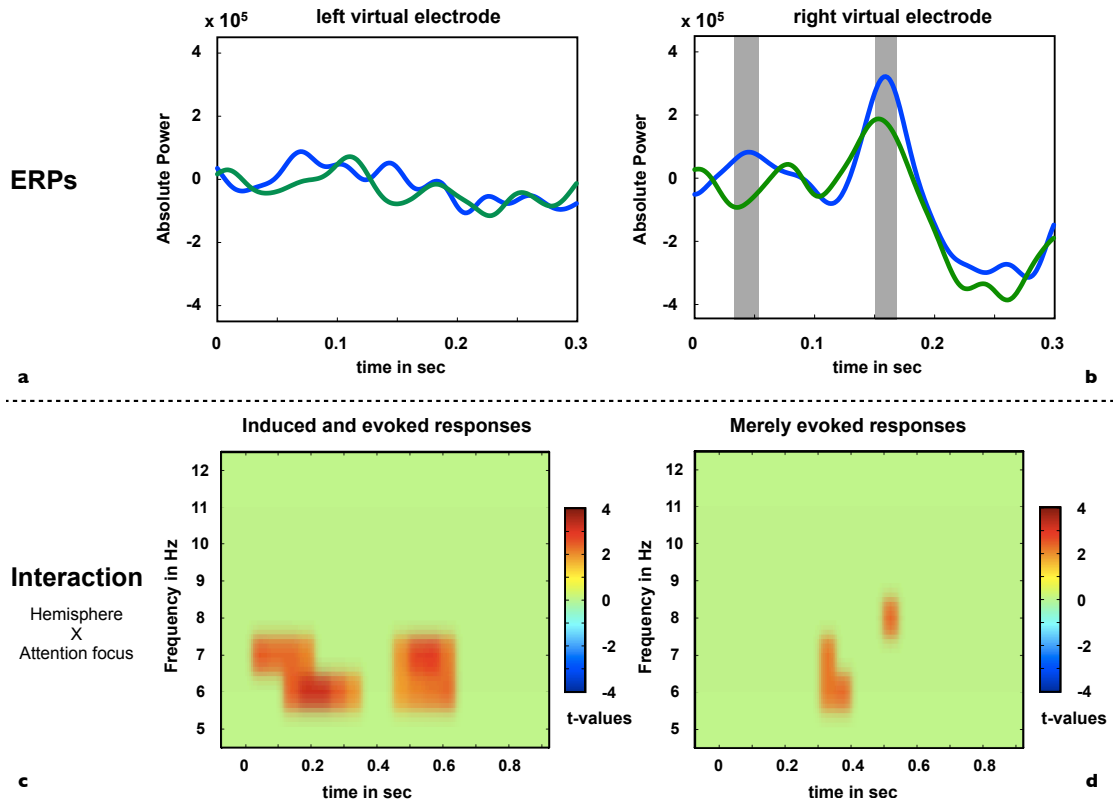


Figure 1: *a/b*: Evoked responses at the left and right auditory virtual electrodes following a visual cue. The averaged responses following a right cue are shown in blue while the averaged responses elicited by a left cue are depicted in green. Particularly for the right auditory cortex we found surprisingly strong evoked responses, which were more pronounced when attention was directed to the ipsilateral right ear. Shown are absolute changes from baseline to the cue-stimulus interval (cue-onset at 0 ms). Grey bars indicate significant differences between conditions (attend right vs. left) *c*: Interaction between hemisphere and attentional focus for the time-frequency representations, masked by p<.05. Evoked and induced responses are not separated. *d*: Interaction between hemisphere and attentional focus for the evoked time-frequency representations, masked by p<.05. Note that the evoked response contributes significantly to the described interaction effect (shown on the left, *c*), however, only within a short time window (300–400 ms) and to a less strong extent

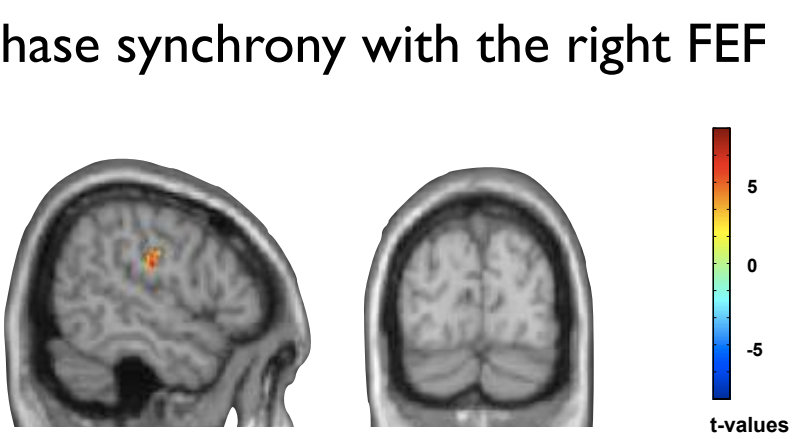
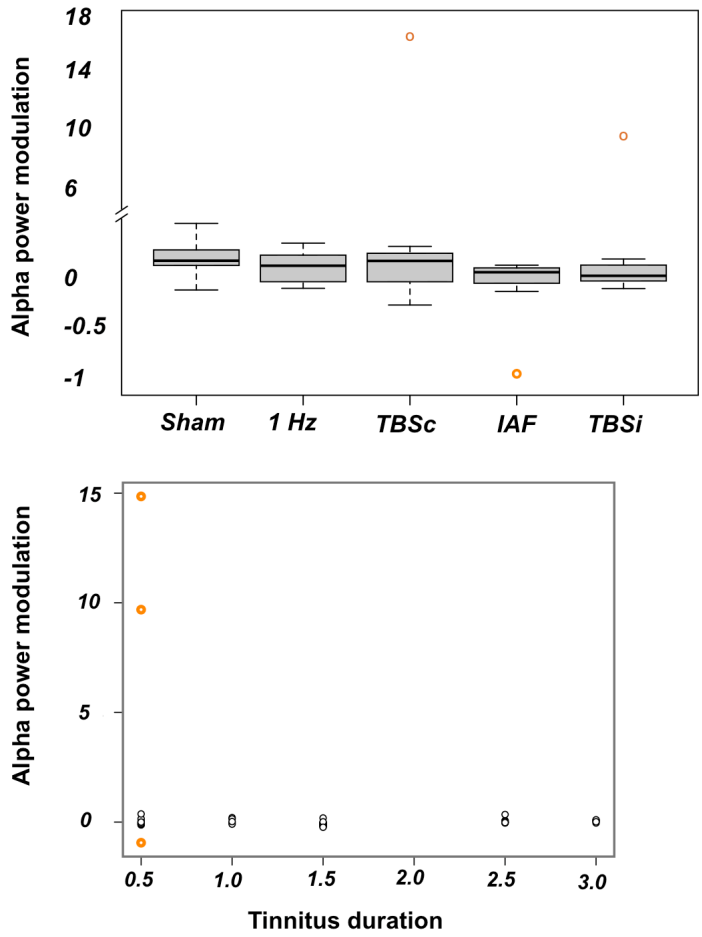


Figure 2: Phase synchrony (5 Hz) of the right FEF. Displayed are the modulations of phase synchrony with the right FEF for the two attention conditions (attend right vs. left), expressed in t-values and masked with a p-value <. 01. Shown are the regions that significantly modulate their phase synchrony for the two attention conditions with the right FEF. After correction for multiple comparisons four regions remained that exhibited significant differences in phase coupling with the right FEF dependent on the attentional focus (the right auditory cortex as expected, a region close to left Brodman area 13, an inferior frontal and a medial frontal region). Importantly, phase synchrony of the visual cortex with the FEFs did not differ between conditions.

Study 2:



Boxplot distribution for the different TMS protocols

symbol for outliers

Relation between tinnitus duration and alpha power modulation

Figure 1: Distribution of extreme values, exemplary for *alpha* power modulations. The upper panel illustrates a boxplot distribution of the data for the different rTMS protocols. Extreme values were detected after cTBS, IAF rTMS and iTBS, and not after 1-Hz rTMS and sham. The lower panel illustrates the relation between tinnitus duration and auditory alpha power modulation. Extreme values are exclusively associated with very short tinnitus duration.

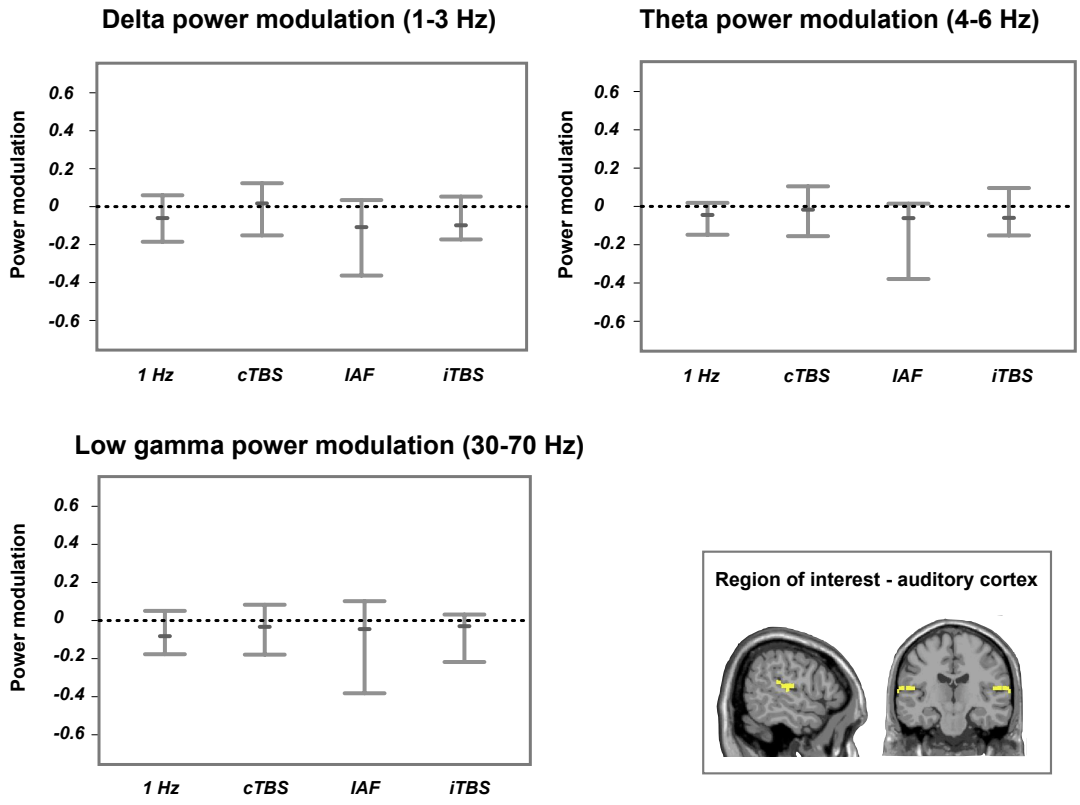


Figure 2: Consistent changes in oscillatory activity after the four active TMS protocols (1 Hz rTMS, cTBS, IAF rTMS, iTBS) compared to sham. The upper left panel displays delta power modulations, the upper right panel illustrates theta power modulations and the lower left panel shows modulations of low gamma power at the stimulated auditory cortex. The stimulated region and region of interest is displayed on the lower right side. Shown are the 95% confidence intervals. The small bars display the median. No significant power modulations were found either in the delta, theta or in the low gamma band.

Study 3:

Table 1: Additional data - ECoG Patients.

subject	sex	age	site of lesion	lesion	surgery	outcome	AED
1	m	12	l. parietal	FCD	extented lesionectomy	seizure-free	LEV, LTG
2	f	17	r. frontal	FCD	inoperabel	-	LEV, LTG

3	m	39	l. frontal	cavernoma	surgery declined	-	LEV
4	f	47	r. temporal	AHS	SAH	seizure-free	LEV, PHT
5	f	18	r. temporal	AHS	temporal lobectomy	occasional auras	CBZ
6	f	13	r. temporo-occipital	FCD	extented lesionectomy	seizure-free	LEV, LTG

l. = left, r. = right; SAH = selective amygdalo-hippocampectomy; AED = antiepileptic drugs, LEV = levetiracetam, LTG = lamotrigine, PHT 0 phenytoin, CBZ = carbamazepine

Table 2: List of intracranial electrodes.

Patient	Cluster number	Cluster p-value	MNI coordinates	Frequency range	Time period	Mean t-value
1	-	-	-	-	-	-
2	1	.016	56 -2 -29	10 20	1350 1400	NaN
			63 -9 -22	9 20	1350 1450	NaN
			67 -16 -14	5 20	1150 1650	NaN
			64 -34 6	7 11	1300 1400	-2.5290
			63 -42 14	9 12	1300 1400	-2.1792
			55 5 -19	8 10	1450 1500	NaN
			61 -2 -13	8 11	1450 1550	-2.6337
			65 -10 -4	5 17	1150 1550	NaN
			65 -18 4	6 14	1150 1650	-2.1125
			65 -26 14	5 11	1150 1600	NaN
			64 -34 22	8 12	1200 1400	-2.3355
			60 -41 31	10 12	1300 1350	NaN
3	-	-	-	-	-	-
4	1	0	10 -42 81	7 20	500 1900	NaN
			12 -31 84	7 20	550 2000	NaN
			12 -19 82	6 20	800 2000	NaN
			13 -8 80	6 20	650 2000	NaN
			14 4 81	7 20	500 1450	NaN
			11 14 76	9 20	500 1300	NaN
			11 23 69	12 12	550 550	NaN
			12 35 67	11 11	1450 1450	NaN
			20 -46 81	7 20	650 1800	NaN
			22 -35 80	6 20	500 1900	NaN
			22 -22 78	7 20	500 1500	NaN
			23 -9 76	5 14	500 1550	NaN
			23 3 74	7 20	500 1350	NaN
			21 14 69	9 11	1250 1400	-2.0282

			21 24 64	7 20	500	700	-2.3032
			21 36 62	10 13	1350	1450	-2.1003
			30 -46 75	6 20	550	1600	NaN
			34 -35 75	6 20	550	1800	NaN
			33 -23 73	5 20	500	1900	NaN
			33 -11 70	5 20	500	1700	NaN
			33 2 68	7 17	800	1900	NaN
			32 14 65	6 8	650	1750	NaN
			31 25 60	7 20	600	1350	NaN
			31 37 58	9 12	850	1400	NaN
			39 -48 68	6 20	850	1600	NaN
			44 -37 69	6 20	850	1450	NaN
			45 -25 68	6 13	500	1750	NaN
			44 -12 64	5 14	500	1950	-2.0807
			44 1 61	5 20	500	1950	-2.6112
			42 14 59	5 20	500	1800	-2.2345
			40 25 54	6 20	500	1500	NaN
	2	.034	12 -19 82	4 4	-150	150	-2.1865
			13 -8 80	7 7	200	200	NaN
			22 -22 78	20 20	-100	-100	NaN
			23 -9 76	4 15	-200	150	NaN
			23 3 74	5 7	-200	200	NaN
			33 -23 73	7 10	100	250	NaN
			33 -11 70	8 20	-100	100	NaN
			33 2 68	5 15	-500	50	NaN
			32 14 65	5 5	-150	-50	-2.1165
			44 -37 69	5 5	-200	-100	-2.0534
			45 -25 68	5 5	-200	-50	-2.4355
			44 -12 64	4 16	-200	300	NaN
			44 1 61	4 20	-350	400	-2.1852
			42 14 59	4 20	-200	400	NaN
			40 25 54	7 8	0	150	-2.5988
5	1	0	40 -4 -54	3 20	550	1800	NaN
			55 -14 -58	3 20	500	2150	NaN
			68 -21 -47	3 15	450	2150	NaN
			79 -30 -35	3 9	450	2150	NaN
	2	0	-39 -4 -59	6 15	200	700	-2.1387
			-56 -10 -61	6 15	200	700	NaN
			-70 -12 -49	6 10	300	700	-2.3905
			-81 -16 -36	6 10	300	650	-2.1814
	3	.02	-39 -4 -59	5 10	1900	2400	NaN
			-56 -10 -61	5 10	1900	2400	NaN
			-70 -12 -49	7 9	2200	2300	-2.0007
			-81 -16 -36	7 9	2200	2300	-2.3122
	4	.02	23 -55 -15	9 11	-450	-350	-2.4779
			37 -48 -20	8 11	-500	-350	-2.6644
			49 -45 -24	8 13	-500	-350	-2.6936
			61 -40 -27	8 13	-500	-400	-2.2486