



## Targeting the Parahippocampal Area by Auditory Cortex Stimulation in Tinnitus



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### ARTICLE INFO

#### Article history:

Received 16 September 2013

Received in revised form

9 April 2014

Accepted 9 April 2014

Available online 14 August 2014

#### Keywords:

EEG

sLORETA

Functional connectivity

Phase synchronization

Gamma

Auditory cortex

Tinnitus

Electrodes

### ABSTRACT

**Background:** The final common pathway in tinnitus generation is considered to be synchronized auditory oscillatory hyperactivity. Intracranial auditory cortex stimulation (iACS) via implanted electrodes has been developed to treat severe cases of intractable tinnitus targeting this final common pathway, in the hope of being a panacea for tinnitus. However, not everybody responds to this treatment. Objective: The electrical brain activity and functional connectivity at rest might determine who is going to respond or not to iACS and might shed light on the pathophysiology of auditory phantom sound generation.

**Method:** The resting state electrical brain activity of 5 patients who responded and 5 patients who did not respond to auditory cortex implantation are compared using source localized spectral activity (Z-score of log transformed current density) and lagged phase synchronization.

**Results:** sLORETA source localization reveals significant differences between responders vs non-responders for beta3 in left posterior parahippocampal, hippocampal and amygdala area extending into left insula. Gamma band differences exist in the posterior parahippocampal areas and BA10. Functional connectivity between the auditory cortex and the hippocampal area is increased for beta2, delta and theta2 in responders, as well as between the parahippocampal area and auditory cortex for beta3.

**Conclusion:** The resting state functional connectivity and activity between the auditory cortex and parahippocampus might determine whether a tinnitus patient will respond to a cortical implant. The auditory cortex may only be a functional entrance into a larger parahippocampal based tinnitus network.

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### Introduction

Non-pulsatile tinnitus is considered to be an auditory phantom percept [1] analogous to phantom pain [2,3]. Both phantom percept disorders have been considered persisting aversive memory traces [4] and share similar clinical features, pathophysiological mechanisms and treatment approaches [2–5]. It is a frequent symptom

with an incidence of about 1% and prevalence of 10–15% in the western world [6,7]. There are little to no effective evidence-based treatments [8]. It severely impairs the quality of daily life in 2–3% of the population [7], and is often associated with insomnia [9], anxiety [10,11] and depression [11,12].

A pathophysiological model, called thalamocortical dysrhythmia, based on sensory deprivation, has been proposed both for pain and tinnitus [13]. At rest, in a normally functioning auditory system without deafferentation, the auditory thalamocortical columns oscillate at alpha frequencies (8–12 Hz). When there is deafferentation (hearing loss) alpha oscillations decrease to theta (4–7 Hz), possibly because there is less information to be processed [14]. This increased hearing loss associated theta activity results in decreased GABA<sub>A</sub> (gamma amino butyric acid) mediated lateral inhibition [13,15] leading to a halo of faster gamma band activity (30–80 Hz) at the lesion edge, generating the positive symptoms (tinnitus, pain). This pathologically persisting coupled theta-gamma rhythm is called thalamocortical dysrhythmia [13].

Financial disclosure: This research was supported by a research grant of St Jude Medical. The company had no influence on the study design, patient selection, data analysis nor on the content of the manuscript.

Conflict of interest: The authors have no conflict of interest with regards to the outcomes in this manuscript. DDR holds a patent on burst stimulation, mentioned in this manuscript.

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Magnetoencephalography (MEG) studies have demonstrated that tinnitus is indeed correlated to decreased alpha [16] and associated increased gamma band activity in the contralateral auditory cortex [13,17]. Furthermore, the amount of contralateral gamma band activity correlates with the perceived intensity of the phantom sound [18]. Gamma band activity (local field potentials and firing rate) in the auditory cortex correlates to the BOLD signal on fMRI [19,20], and recordings from implanted electrodes overlying the secondary auditory cortex in a tinnitus patient has demonstrated that gamma activity correlates with the BOLD signal and that theta and gamma are coupled in the tinnitus state [21]. Based on the above data it has been suggested that fMRI can be used clinically as an indirect way of looking at the neural signature of tinnitus [22]. And indeed, recordings from an implanted electrode have revealed that maximal tinnitus suppression is obtained by current delivery exactly at the BOLD spot, which co-localizes with increased spatially coupled gamma and theta activity in contrast to the other electrode poles demonstrating a normal alpha peak. These spectral changes normalize when stimulation induces tinnitus suppression, both on electrode and source localized EEG recordings. These data suggest that theta-gamma coupling as proposed by the thalamocortical dysrhythmia model might be causally related to a conscious auditory phantom percept [21].

It has been demonstrated that electrical stimulation via implanted electrodes [5,23–28] on the auditory cortex in humans can benefit some patients suffering from tinnitus by interfering with the proposed thalamocortical dysrhythmia model [21,28]. However, in a recent evaluation of more than 40 implanted tinnitus patients it was shown that only 1 out of 3 of these patients responded to tonic stimulation and that 50% of non-responders to tonic stimulation could be rescued by applying burst stimulation, still resulting in 1/3 patients not responsive to the implant [29]. Since all implanted patients responded twice to a TMS session in a placebo-controlled way, this TMS test is not ideal as a predictive test for selecting patients for surgical implantation. On the other hand, if a patient responds to the implant, the amount of tinnitus suppression obtained by TMS does correlate with the amount of tinnitus suppression obtained by the implant [29].

It remains elusive why some patients do respond to the implant and others do not, even though correct surgical positioning is verified by fusion of the postoperative CT scan (demonstrating the exact localization of the electrode) with the preoperative fMRI

(demonstrating the most likely auditory cortex generator of the tinnitus). One can hypothesize that some people are more resistant to electrical stimulation than others. This is in accordance with data from transcranial direct current stimulation [30,31], transcranial magnetic stimulation [32–34] and transcutaneous electrical nerve stimulation [35] in tinnitus, with a response rate of 30–50% of patients. The aim of the study is to determine whether differentiating the resting state brain activity and functional connectivity on a preoperative EEG with source analysis might help to predict successful implantation for tinnitus suppression, and might be clinically relevant as an adjunct for selecting future candidates for implants.

## Methods and materials

### Participants

Participants were selected from a group of patients who had been implanted with an electrode overlying the posterior part of the superior temporal gyrus, i.e. the secondary auditory cortex in an attempt to treat their tinnitus. Details about the selection criteria and surgical technique have been published before [23,24,29,36]. In brief, if a treatment intractable patient responds on two separate days to transcranial magnetic stimulation in a placebo-controlled way, targeting the superior temporal gyrus, the patient was eligible for an extradural implant. Intractable means the patient has no lasting benefit from audiological or ENT treatments and has no improvement from medication (flupentixol, melitracen and clonazepam) [37]. The electrode was targeting the area of BOLD activation on fMRI, elicited by presenting tinnitus matched sound in the MRI scanner, as described before [29]. The surgery is aided by fMRI guided intraoperative neuronavigation [21,22,24,29]. The side of the implant was contralateral for unilateral tinnitus and the side that yielded most suppression for bilateral tinnitus. One patient underwent bilateral implantation (patient no. 8). The BOLD spot used as the surgical target correlates to theta-gamma band coupled activity on source analyzed EEG [21] (group data submitted).

Ten patients (6 male, 4 female, mean age = 47 years, range = 26–63 years, see Table 1 for detailed information) who had preoperative EEGs performed were selected from the multidisciplinary Tinnitus Research Initiative (TRI) Clinic of the University Hospital of Antwerp, Belgium. Data were retrospectively collected that detailed the patients' gender, age, tinnitus type, tinnitus side,

**Table 1**  
Patient characteristics.

Subject	Responder	Sex	Age	Tinnitus type	Tinnitus side	Tinnitus pitch (Hz)	Tinnitus intensity (dB SL)	Tinnitus loudness (VAS)	Tinnitus grade	Side of implant	Tinnitus duration (years)
1	R	M	54	PT + NBN	R	6000	7	9	III	L	1
2	R	M	34	NBN	R	6000	0	8	IV	R	3
3	R	V	63	NBN	R > L	6000	0	9	IV	L	17
4	R	M	45	NBN	L > R	3000 L 4000 R	5 5	9 6	IV	R	18
5	R	M	45	NBN	R	6000	10	9	III	R	1
Responders	<i>Mean</i> <i>SD</i>		48.20 11.55			5166.67 1329.16	4.50 3.93	8.33 1.12			8.00 8.17
6	NR	M	49	PT	BIL	6000	3	9	IV	L	3
7	NR	V	42	PT	L	2000	20	10	II	R	4
8	NR	M	52	NBN	R > L	16000	10	7	III	L + R	3
9	NR	V	62	PT	BIL	8000	X	8	X	R	1
10	NR	V	26	PT	R	8000	65	8	III	L	1
Non-responders	<i>Mean</i> <i>SD</i>		46.20 13.38			80,000 5099.02	19.60 26.52	8.40 1.14			2.40 1.34
R vs NR			$U = 11$ $P = .84$			$U = 8$ $P = .25$	$U = 9.5$ $P = .33$	$U = 14$ $P = .93$	$\chi^2 = 5.11$ $P = .28$		$U = 10$ $P = .69$

R = responder, NR = non-responder, PT = pure tone tinnitus, NBN = narrow band noise tinnitus, L = left, R = right, BIL = bilateral.

tinnitus pitch, tinnitus loudness, tinnitus distress grade, tinnitus duration, side of the implant, hearing loss at the tinnitus frequency and type of hearing loss. Tinnitus type is specified as pure tone, narrow band noise or a combination of both types. No patient had polyphonic tinnitus. Tinnitus side is specified as right side, left side or both sides. No patient had holocranial tinnitus (perceived as inside the entire head). Tinnitus pitch and loudness is determined by tinnitus matching analysis, as explained previously [38]. In brief, patients with unilateral tinnitus are presented tones in their contralateral non-tinnitus ear and have to match it to the tone of the perceived tinnitus. Subsequently the sound level is increased until the patient claims that the presented tone or noise matches the tinnitus perfectly. In bilateral tinnitus this is performed by a similar approach, where the patient has to state at what time he/she cannot distinguish the presented sound from the tinnitus. Tinnitus grading is performed by the use of a validated Dutch version [39] of the Tinnitus Questionnaire [40]. This separates the severity of the tinnitus distress in 4 grades: grade I: not distressing, grade II: moderate distress, grade III: severe distress, grade IV: very severe distress. Hearing loss at the tinnitus frequency is specified as most pathophysiological models propose that tinnitus is a phantom percept related to deafferentation or hearing loss and that the tinnitus frequency (pitch) matches the frequency of hearing loss [4,41]. The type of hearing is specified as well: no hearing loss, audiometric dip at specific frequencies and presbycusis type hearing loss. An audiometric dip is a hearing loss limited to very few frequencies with normal thresholds for the rest of the audiometry. Presbycusis is a bilateral symmetrical sensorineural hearing loss characterized by normal or minimal hearing loss at low frequencies and progressively worsening hearing loss at higher frequencies. Patients were considered non-responders if neither tonic nor burst stimulation could reduce the tinnitus loudness perception by more than 3-points on a numeric rating scale for loudness (0 = no tinnitus, 10 = loudest tinnitus imaginable) after 6 months of treatment.

For the EEG measures, participants were requested to refrain from alcohol consumption 24 h prior to recording, and from caffeinated beverages consumption on the day of recording. Patient's subjective tinnitus loudness perception was obtained on a Visual Analogue Scale (VAS) from 0 to 10 (mean VAS score = 8.36, range = 6–10). After one year of therapy the mean VAS was 7.5 (range = .5–9). Responders had a mean reduction of 66.67% after 6 months of treatment, while the non-responders had a mean reduction of 9%. No significant differences were obtained between the responders and non-responders on age, gender, distress, hearing loss, tinnitus pitch, tinnitus intensity, duration and hearing loss at the tinnitus frequency.

The retrospective study was approved by the Ethical Committee of the University Hospital of Antwerp, Belgium.

#### EEG data collection

Resting state electroencephalographic (EEG) signals were recorded continuously according to the 10–20 system. EEG activity was obtained over 5 min with eyes closed using a digital EEG (Neuroscan, Compumedics, Houston, TX) in a dimly illuminated and sound-isolated room (sampling rate = 1000 Hz, band passed .15–200 Hz). Electrodes were referenced near the vertex and impedances were checked to remain below 5 k $\Omega$ . The following 19 electrodes were included in later analysis (Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1 and O2). Electro-oculogram (EOG) was recorded for artifact detection.

EOG artifacts were removed in Matlab (The Mathworks, Natick, MA) using the automatic artifact removal toolbox in EEGLAB (<http://sccn.ucsd.edu/eeeglab/index.html>). Data were band-passed

filtered to 1–45 Hz and subsequently exported for further visual inspection and source analysis to Eureka3! (Nova Tech EEG, Inc.).

#### sLORETA imaging

Standardized low-resolution brain electromagnetic tomography (sLORETA) [42] was used to estimate the intracerebral electrical sources that generated the scalp-recorded activity in each of the seven frequency bands. sLORETA computes electrical neuronal activity as current density (A/m<sup>2</sup>) without assuming a predefined number of active sources. The sLORETA solution space consists of 6239 voxels (voxel size: 5 × 5 × 5 mm) and is restricted to cortical gray matter including hippocampi, as defined by the digitized Montreal Neurological Institute probability atlas. To reduce confounds that have no regional specificity, such as total power inter-subject variability, a global normalization of the sLORETA images was carried out prior to statistical analyses.

#### Lagged phase synchronization

Phase synchronization between time series corresponding to different spatial locations are usually interpreted as indicators of the “functional connectivity.” However, any measure of dependence is highly contaminated with an instantaneous, non-physiological contribution due to volume conduction and low spatial resolution [43]. Therefore Pascual-Marqui et al. [43] introduced a new technique (i.e. Hermitian covariance matrices) that removes this confounding factor considerably. As such, this measure of dependence can be applied to any number of brain areas jointly, i.e. distributed cortical networks, whose activity can be estimated with sLORETA. Measures of linear dependence (coherence) between the multivariate time series are defined. The measures are expressed as the sum of lagged dependence and instantaneous dependence. The measures are non-negative, and take the value zero only when there is independence of the pertinent type and are defined in the frequency domain: delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10–12.5 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz) and gamma (30.5–45 Hz). Based on this principle lagged linear connectivity was calculated. Regions of interest were the left and right primary (BA40 and BA41) and left and right secondary auditory cortex (BA21 and BA22), the left and right parahippocampal (BA27, B28, BA34, BA35) area.

#### sLORETA and lagged phase synchronization analysis

In order to identify potential differences in brain electrical activity between responders and non-responders, sLORETA was then used to perform voxel-by-voxel between-condition comparisons of the current density distribution. Nonparametric statistical analyses of functional sLORETA images (statistical non-parametric mapping; SnPM) were performed for each contrast employing a t-statistic for unpaired groups and corrected for multiple comparisons ( $P < .05$ ). As explained by Nichols and Holmes, the SnPM methodology does not require any assumption of Gaussianity and corrects for all multiple comparisons [44]. We performed one voxel-by-voxel test (comprising 6239 voxels each) for the different frequency bands.

## Results

#### Source analysis

sLORETA showed significant differences between responders and non-responders to auditory cortex implants. Increased synchronized beta3 band activity could be revealed in the left parahippocampal area (BA27, 28, 34, 35) extending to the hippocampus,

amygdala and left insula for responders. For gamma, increased activity is noted in the parahippocampus bilaterally associated with decreased activity prefrontally (BA10) (see Fig. 1;  $P < .05$ ). No significant differences could be retrieved in the delta, theta, alpha1, alpha2, beta1, and beta2 frequency bands.

#### Lagged phase synchronization

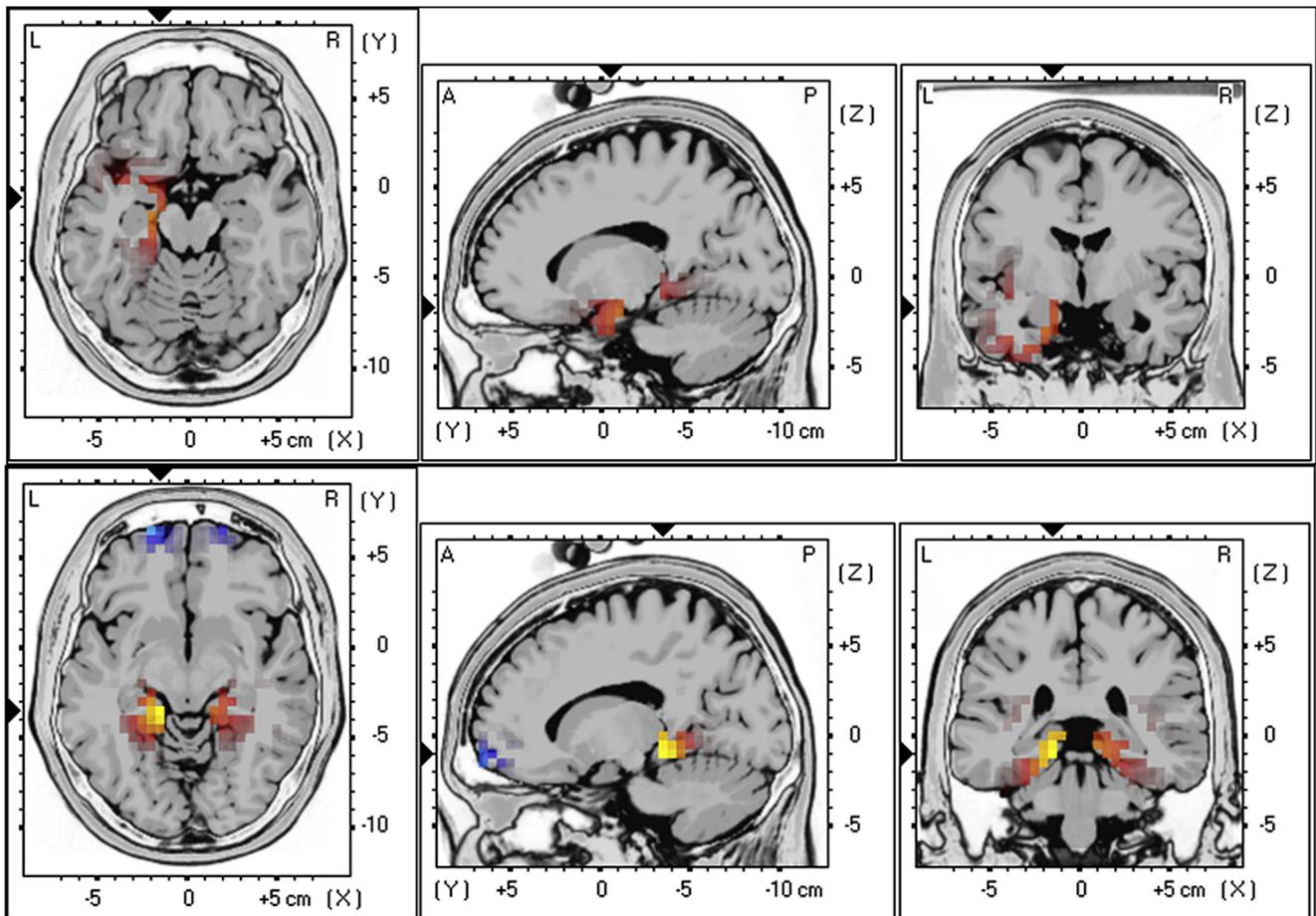
Functional connectivity analysis demonstrated increased significant ( $P < .05$ ) lagged phase synchronization for the delta, theta, beta2 and beta3 frequency band for responders in comparison to non-responders (see Figs. 2 and 3). A closer look revealed that for delta an increased lagged phase synchronization is found between the left secondary auditory cortex and right parahippocampus for responders. For the theta frequency band increased lagged phase synchronization was revealed between the right parahippocampus, left parahippocampus and the left secondary auditory cortex for responders, while for the beta2 frequency band increased synchronization was found between the right primary auditory cortex and the right parahippocampus. For beta3 the right parahippocampal area was phase synchronized with respectively the left parahippocampus, the right primary and secondary auditory cortex and the left secondary auditory cortex in responders. Also the left parahippocampus was phase synchronization with the right primary auditory cortex, the left secondary auditory cortex and the right parahippocampus. In addition more lagged phase

synchronization was revealed between the left primary auditory cortex and the right secondary auditory cortex and between the left and right primary auditory cortex for responders.

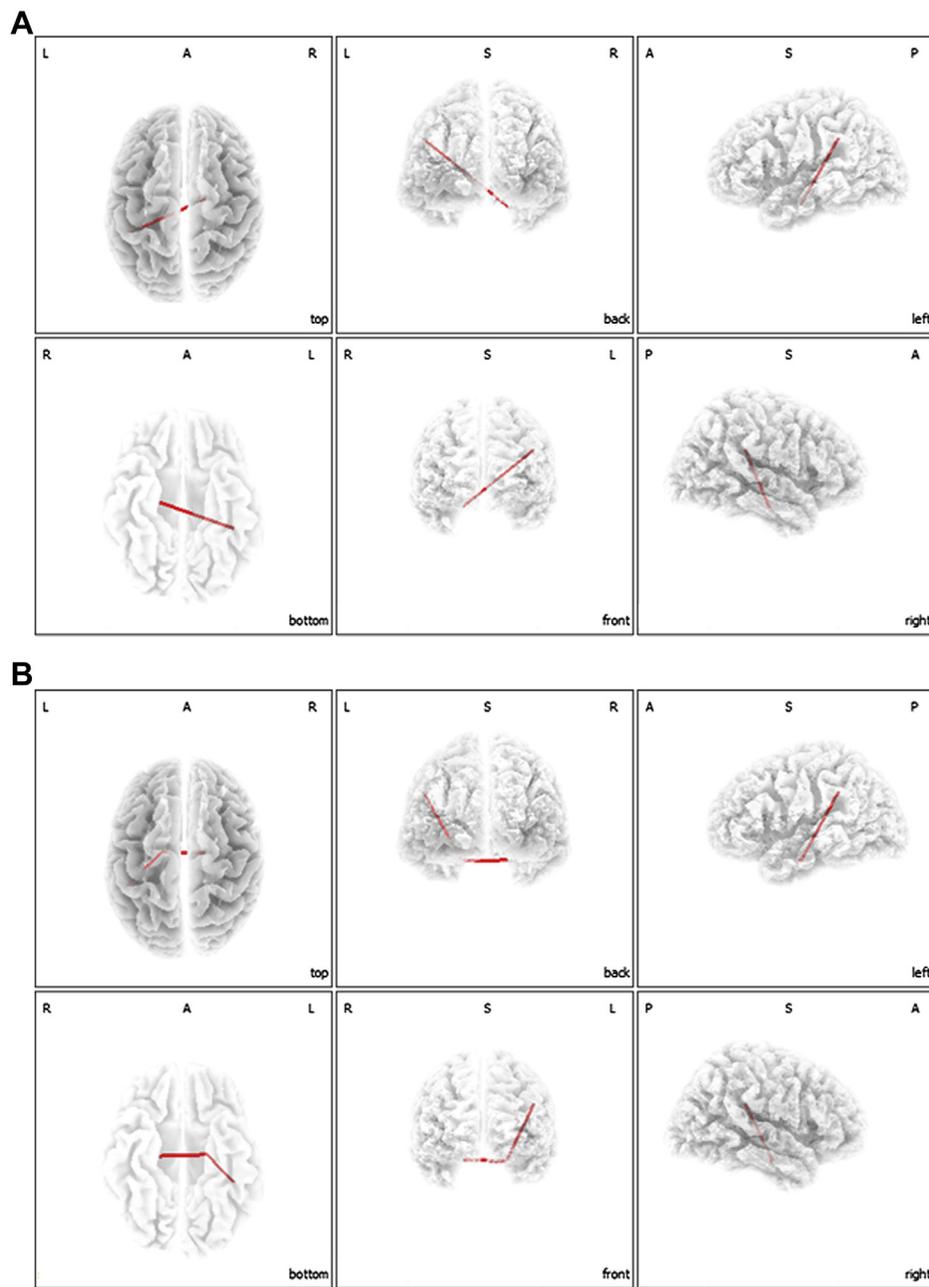
#### Discussion

The main objective of this study was to characterize the differences in resting state brain activity and functional connectivity as measured by source analyzed EEGs in tinnitus patients who are going to respond to auditory cortex implants for tinnitus suppression in comparison to patients who are not going to respond to the surgery.

In contrast to our expectation, which was that responders and non-responders would show differences in auditory cortex activity, differences were demonstrated in left and right parahippocampal areas for gamma, and in the left amygdala-hippocampal-parahippocampal area extending into the left insula for beta3. However, the electrodes were implanted extradurally overlying the secondary auditory cortex. It is difficult to understand that whether or not you will respond to auditory cortex stimulation is determined by activity in the parahippocampal area. Conceptually the parahippocampal area can determine responsiveness to auditory cortex stimulation for tinnitus suppression only if 1) the current can get from the auditory cortex to the parahippocampal area and 2) the parahippocampal area is involved in the pathophysiology of tinnitus. Therefore we analyzed functional connectivity between



**Figure 1.** Whole brain EEG analysis with sLORETA source analysis, comparing responders to non-responders to auditory cortex stimulation. Responders have more Beta3 activity in the left parahippocampal area, hippocampus and amygdala, extending into left insula (upper panel). Responders have more gamma band activity in the posterior parahippocampal area bilaterally and less in the frontopolar cortex (BA10) (lower panel).

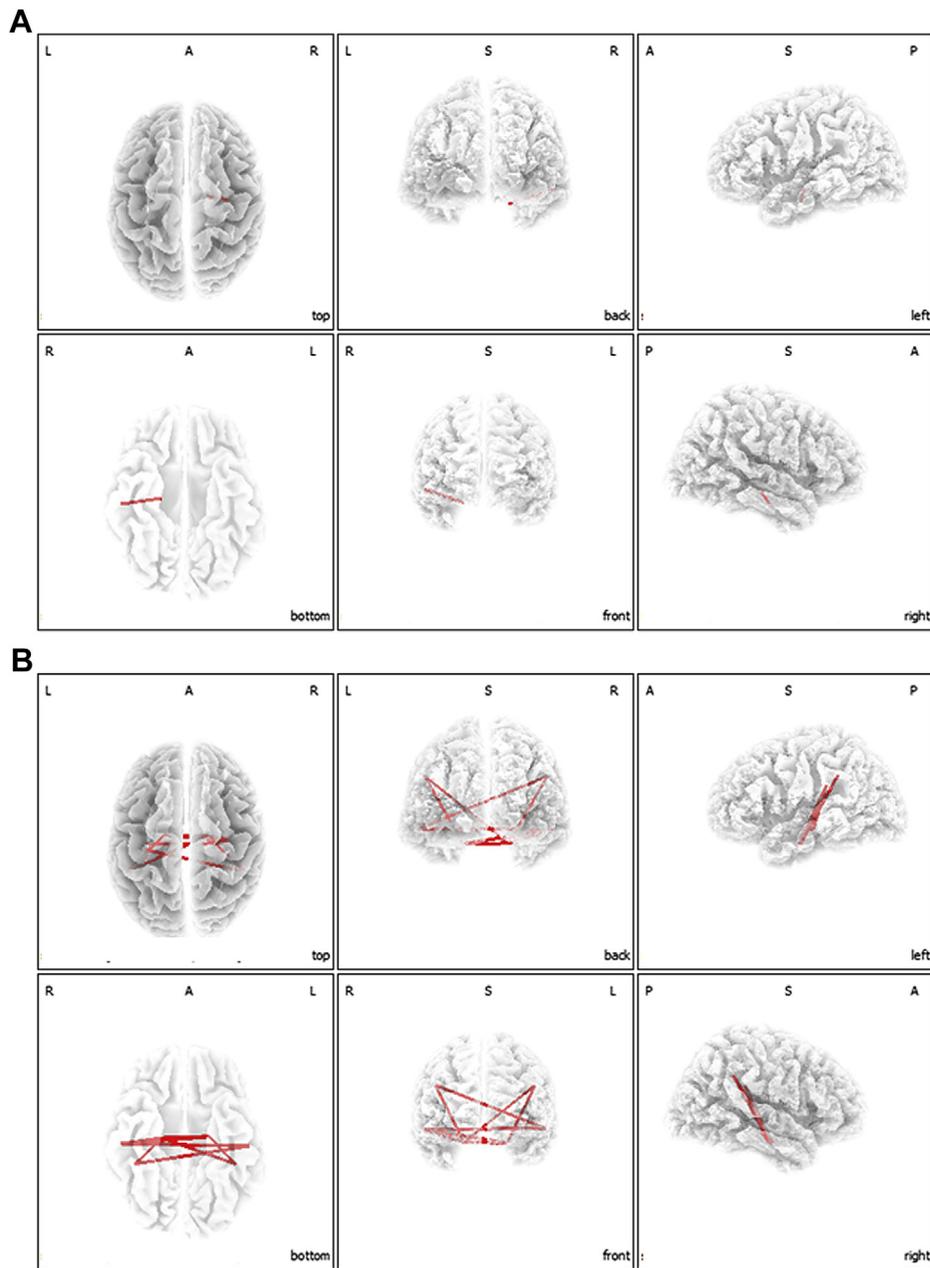


**Figure 2.** Functional connectivity as measured by lagged phase synchronization for the delta (A) and theta2 (B) frequency band in sLORETA source space. (A) For delta an increased lagged phase synchronization is found between the left secondary auditory cortex and right parahippocampus for responders. (B) For the theta frequency band increased lagged phase synchronization was revealed between the right parahippocampus, left parahippocampus and the left secondary auditory cortex for responders.

auditory cortex and hippocampal/parahippocampal area established a difference in the functional connectivity with increased lagged phase synchronization for the delta, theta2, beta2 for responders between the auditory cortex and the hippocampus, but especially the beta3 band between the auditory cortex and parahippocampal area for responders.

This suggests that the mechanism of action is not via suppression of increased synchronized gamma band activity in the auditory cortex, which is hypothesized to be the final common pathway for tinnitus, but via an indirect modulation of high frequency activity (beta3 and gamma) in the parahippocampus. Only patients who have good functional connectivity between the stimulated auditory cortex and the parahippocampal area benefit from the stimulation.

The parahippocampal involvement in sensitivity to electrical brain stimulation might be related to its auditory sensory gating function. Electrophysiological recordings in humans implanted with electrodes for epilepsy monitoring demonstrated that auditory sensory gating is mediated by a network, which includes the auditory cortex, prefrontal cortex and the parahippocampus [45–48]. Sensory gating involves suppression of redundant or irrelevant auditory information, and the parahippocampus is considered the entry to the auditory hippocampus [49]. Based on results of tinnitus suppression via supraselective amygdala testing of the anterior choroidal artery which supplies the amygdalohippocampal area, it has been hypothesized that the hippocampus could be constantly updating the tinnitus which is being generated in the thalamocortical system [50] preventing habituation. Cells in the



**Figure 3.** Functional connectivity as measured by lagged phase synchronization for the beta2 (A) and beta3 (B) frequency band in sLORETA source space. For the beta2 frequency band increased phase synchronization is found between the right primary auditory cortex and the right parahippocampus in responders. For beta3 the right parahippocampal area is phase synchronized with respectively the left parahippocampus, the right primary and secondary auditory cortex and the left secondary auditory cortex in responders. Also the left parahippocampus is phase synchronized with the right primary auditory cortex, the left secondary auditory cortex and the right parahippocampus. In addition more lagged phase synchronization is revealed between the left primary auditory cortex and the right secondary auditory cortex and between the left and right primary auditory cortex for responders.

human hippocampus and parahippocampal areas respond to novel stimuli with an increase in firing. However, already on the second presentation of a stimulus, neurons in these regions show very different firing patterns. In the parahippocampal region there is dramatic decrease in the number of cells responding to the stimuli [51], suggesting a rapid habituation. This rate of response decrement during trains of several stimulus repetitions is linear for acoustic responses [52]. In contrast to the rapid auditory habituation in the parahippocampal area, in the hippocampus there is recruitment of a large subset of neurons showing inhibitory responses [51]. Repetitive auditory stimuli both in animals [53] and humans lead to attenuation of event related responses (ERPs), but

with differences in hippocampal and parahippocampal areas, as early hippocampal ERPs are not attenuated, in accordance with the abovementioned single cell recordings. Thus a novel stimulus normally is associated with parahippocampal habituation and active hippocampal inhibitory activity. Based on these data it can be hypothesized that in tinnitus this mechanism is disrupted with persistent parahippocampal activity, preventing habituation. The parahippocampal area has been hypothesized to play a central role in memory recollection, sending information from the hippocampus to the association areas, and a dysfunction in this mechanism is posited as an explanation for complex auditory phantom percepts such as auditory hallucinations [54].

It is very interesting that all the patients who respond in this study are the patients who have a hearing loss characterized by an audiometric dip, and where the tinnitus frequency matches the frequency of hearing loss, i.e. those patients where the tinnitus can be attributed to the auditory deprivation. This fits perfectly well with a recently proposed pathophysiology based on a Bayesian brain model [55]. This model states that the brain will fill in the missing information in order to reduce auditory uncertainty. It will do so in different phases depending on the amount of deafferentation. In little deafferentation without hearing loss, the missing input will be retrieved from the cortical neighborhood, either by reduction of lateral inhibition or map plasticity. If that is not possible because the deafferentation is too large, the brain will access auditory memory via the parahippocampal area to fill in the missing information [55]. Also the patient with presbycusis falls under this model, as his tinnitus pitch matches the hearing loss. The non-responders either had no hearing loss, or hearing loss that cannot be linked to the tinnitus pitch, except for patient no. 6 who has presbycusis and hearing loss that matches the tinnitus frequency. A hypothetical explanation why he doesn't respond will be detailed later in the text.

As mentioned, the auditory cortex might only be an entry into a larger parahippocampal based tinnitus network, and the beneficial effect of the implanted electrode overlying the auditory cortex might not be related to a local suppressing effect. This fits with the fact that tDCS of the dorsolateral prefrontal cortex can decrease auditory cortex gamma band activity, associated with a decreased tinnitus loudness, possibly mediated via the pregenual and parahippocampal area [56]. Thus there are likely more cortical areas that can be targeted to interfere with the same tinnitus network. Hypothetically, any area that is functionally connected to the tinnitus network could modulate its activity and exert an effect on the tinnitus perception. This fits with a recently proposed tinnitus model that states that the unified tinnitus percept (including loudness, spatial localization, affective and attentional components) is the result of multiple separable dynamically changing but overlapping subnetworks, each with a different oscillatory signature [57]. Some areas involved at different oscillatory frequencies in different subnetworks can be considered hubs, and the parahippocampal area is one of the most important hubs, as it is involved in tinnitus lateralization, mood, distress, and perceptual components of the tinnitus [56–71]. It has been suggested based on network science analysis that targeting these hubs in tinnitus should lead to optimal tinnitus suppression [72], analogous to what has been proposed in general for scale free networks [73]. And indeed, it has been shown that tinnitus improvement resulting from dorsolateral prefrontal cortex stimulation involves the parahippocampus [56,66].

The fact that tinnitus suppression might be more related to parahippocampal activity than auditory cortex activity is reminiscent of what is demonstrated for motor cortex stimulation, where the motor cortex stimulation also exerts its effect by altering activity in functionally connected distant areas [74].

How does the thalamocortical dysrhythmia model fit with these findings? As Llinas suggested the theta activity is related to the auditory deafferentation, i.e. the hearing loss and he suggests the tinnitus is related to the high frequency (beta3 and especially) gamma band activity. However local gamma band activity does not lead to conscious perception. For an auditory stimulus to be consciously perceived, activation of the primary auditory cortex is a prerequisite but not sufficient [75–78]. Studies performed on patients in vegetative state who do not have conscious auditory percepts reveal that auditory stimuli still activate the primary auditory cortex but that there is no functional connectivity to frontal areas in these patients. The 'global workspace' model proposed as model for

conscious perception suggests that conscious perception of sensory events requires sensory cortex activation embedded in a cortical network, called the global workspace, extending beyond the primary sensory regions, including prefrontal, parietal and cingulate cortices [75]. Especially the hippocampal area has been proposed to be an essential hub of the 'global workspace,' propagating thalamocortical activity to the 'global workspace' which permits binding of the thalamocortical activity into unified percept [79]. As the posterior parahippocampal area is the main entry to auditory hippocampal memory, we hypothesize that auditory thalamocortical dysrhythmia only becomes consciously perceived as tinnitus if the cortical gamma band activity is connected to the 'global workspace' via functional connectivity through the parahippocampal gyrus to the hippocampus.

An interesting aspect of this study relates to the fact that all patients responded twice in a placebo controlled way to TMS targeting the posterior aspect of the superior temporal gyrus, i.e. the secondary auditory cortex, as this was a criteria for eligibility to be implanted [24,27,29]. Yet still only half of the patients improve with the implant. Even more interesting is the fact that the electrode implant was based on fMRI BOLD signal elicited by tinnitus frequency matched tone presentation in the scanner. It has been suggested that TMS can be used to turn functional imaging correlations into causal relationships, based on the idea that if the symptom which is correlated to the BOLD signal improves after the TMS session it implies that the area is causally related to the symptom. These results cast doubt on this concept, as the real causal effect could be related to another brain structure functionally connected to the stimulated area. It is well known that TMS has an effect on remote areas as well. Thus it is important to consider that these remote areas might be more important for the behavioral or clinical change induced by TMS than the directly targeted area.

A finding in this study that most responders perceived noise-like tinnitus, which normally is more difficult to suppress by cortical stimulation than pure tone tinnitus [5,22,23,29,36] might seem surprising at first. However, since the development of burst stimulation the amount of tinnitus patients that respond to electrode implants has increased, especially for the patients with noise-like tinnitus [27]. So the fact that most patients who responded were those who perceived noise-like tinnitus is related to the fact that they were treated with burst stimulation, as were the non-responders however. Therefore likely the tinnitus type (pure tone vs narrow band noise) is not relevant as a determining characteristic in this study.

In conclusion, in contrast to our expectation, whether or not a patient responds to cortical stimulation for tinnitus might have less to do with auditory cortex per se, but more with areas the auditory cortex is connected to. The resting state functional connectivity and activity of the brain might therefore determine whether a tinnitus patient will respond to a cortical implant. It is hypothesized that the auditory cortex is only an entrance for neuromodulation into a network centered on the parahippocampus. Future genetic studies should benefit the elucidation of the exact mechanism involved in the expression of this differential functional connectivity. Further analyses on larger groups should also evaluate whether adding clinical criteria might be useful. Especially it should be analyzed whether hearing loss at the tinnitus frequency determines whether or not a patient will respond.

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