Neuroscience 199 (2011) 481–490

CONTRALATERAL PARAHIPPOCAMPAL GAMMA-BAND ACTIVITY DETERMINES NOISE-LIKE TINNITUS LATERALITY: A REGION OF INTEREST ANALYSIS

S. VANNESTE,[a,c]* P. VAN DE HEYNING[b,c] AND D. DE RIDDER[a]

[a]*Brai²n, TRI and Department of Neurosurgery, University Hospital Antwerp, Belgium*

[b]*Brai²n, TRI and ENT, University Hospital Antwerp, Belgium*

[c]*Department of Translational Neuroscience, Faculty of Medicine, University of Antwerp, Belgium*

Abstract—Tinnitus is described as an auditory perception in the absence of any external sound source. Tinnitus loudness has been correlated to sustained high frequency gamma-band activity in auditory cortex. It remains unknown whether unilateral tinnitus is always generated in the left auditory cortex, irrespective of the side on which the tinnitus is perceived, or in the contralateral auditory cortex. In order to solve this enigma source localized electroencephalographic (EEG) recordings of a homogenous group of unilateral left and right-sided tinnitus patients presenting with noise-like tinnitus was analyzed. Based on a region of interest analysis, the most important result of this study is that tinnitus lateralization depended on the gamma-band activity of the contralateral parahippocampal area. As for the auditory cortex no differences were found between left-sided and right-sided tinnitus patients. However, in comparison to a control group both left and right-sided tinnitus patients had an increased gamma-band activity in both the left and right primary and secondary auditory cortex. Thus whereas in tinnitus the primary and secondary auditory cortices of both sides are characterized by increased gamma-band activity, the side on which the tinnitus is perceived relates to gamma-band activity in the contralateral parahippocampal area.

Key words: tinnitus, lateralization, gamma-band activity, parahippocampus, auditory cortex.

Tinnitus is described as an auditory phantom perception (e.g. a tone, hissing, or buzzing sound, and sometimes combinations of such perceptions) in the absence of an external sound source. From time to time almost everyone experiences some form of auditory phantom percept; however, in most cases this sensation disappears within seconds or minutes. In 5–15% of the adult population in western societies tinnitus persists (Heller, 2003). Those patients perceive a constant ringing, buzzing or hissing in the ear which can be quite dominant, especially in a quiet environment. About 1–3% of the entire population (Axelsson and Ringdahl, 1989) or 20% of the patients perceiving tinnitus experience tinnitus with high distress, which has a severe impact on the patients' quality of life. Problems can include anxiety, depression, irritability, agitation, insomnia or depression (Møller, 2007).

Based on magnetoencephalography (MEG), thalamocortical dysrhythmia has been proposed as a pathophysiological model for tinnitus generation (Llinás et al., 1999). According to this pathophysiological model tinnitus is caused by an abnormal, spontaneous and constant gamma-band activity (>30 Hz) generated as a consequence of hyperpolarization of specific thalamic nuclei. In normal circumstances auditory stimuli increase thalamocortical rhythms from alpha to gamma-band oscillations (Joliot et al., 1994). In the deafferented state however, the oscillation rates decrease to theta-band activity (4–7 Hz) (Steriade, 2006). As a result, GABAa-mediated lateral inhibition is reduced, inducing a surrounding coupled gamma-band activity known as the "edge effect." This edge or halo is suggested to be related to the positive symptoms (Llinás et al., 1999, 2005). This theta–gamma coupling has been confirmed by recordings from electrodes overlying the secondary auditory cortex in a tinnitus patient and is only present at the area where the tinnitus is generated (De Ridder, 2010).

Tinnitus perception has indeed been correlated to sustained high frequency gamma-band activity in temporal areas in humans in quantitative electroencephalographic (QEEG) (Ashton et al., 2007) and MEG studies (Llinás et al., 1999, 2005; Weisz et al., 2007). Furthermore the gamma-band activity on EEG correlates with the perceived phantom sound intensity (van der Loo et al., 2009). Weisz et al. propose that hemispheric dominance of tinnitus generation is determined by high frequency activity around 55 Hz in presence of slow-wave activity in the contralateral auditory cortex (Weisz et al., 2007).

An ongoing debate discusses whether tinnitus is always generated in the left or the contralateral auditory cortex. This debate arose because of dissimilar functional imaging results. Functional MRI (Melcher et al., 2000; Smits et al., 2007), MEG (Mühlnickel et al., 1998; Llinás et al., 2005; Weisz et al., 2007) and EEG (van der Loo et al., 2009) suggest the neural generator of the tinnitus is located in the contralateral auditory cortex (Smits et al., 2007) and inferior colliculus (Melcher et al., 2000), whereas most positron emission tomography (PET) studies suggest tinnitus is always generated in the left auditory

*Corresponding author. Tel: +32-821-33-36; fax: +32-3-825-25-28.
E-mail address: sven.vanneste@ua.ac.be (S. Vanneste).

Abbreviations: EEG, electroencephalography; fMRI, functional magnetic resonance imaging; ICA, independent component analysis; MEG, magnetoencephalography; MNI, Montreal Neurological Institute; sLORETA, standardized low-resolution brain electromagnetic tomography; VAS, Visual Analogue Scale.

0306-4522/11 $ - see front matter
doi:10.1016/j.neuroscience.2011.07.067

cortex (Arnold et al., 1996; Eichhammer et al., 2007). But some earlier PET studies show increased metabolic activity in the auditory system of patients with tinnitus on the side contralateral to the side of perceived tinnitus compared with healthy volunteers. Other PET studies however report left-sided auditory cortex activation in predominantly left-sided tinnitus (Andersson et al., 2000) or irrespective of the tinnitus side (Arnold et al., 1996).

Similar findings are demonstrated from modulating the auditory cortex. Several studies have demonstrated that using transcranial magnetic stimulation (TMS) targeting the left auditory cortex irrespective of the lateralization of tinnitus can suppress tinnitus (Langguth et al., 2006b; Kleinjung et al., 2008). Yet other studies using TMS or implanted extradural cortex stimulation reveal that modulating the contralateral auditory cortex to the tinnitus can also suppress tinnitus (De Ridder et al., 2007, 2010). In a recent study it was shown that both left sided and contralateral stimulation exert a beneficial effect but that contralateral stimulation is better than left sided stimulation (De Ridder, 2010; Khedr et al., 2010).

The purpose of our study was to find the neural correlates for tinnitus lateralization. We used source localized EEG recordings of a homogenous group of unilateral left and right-sided tinnitus patients and analyzed the spectral components related to the tinnitus in gamma-band activity. We opt to use only the gamma band as previous research already hypothesized that this band in particular is important for tinnitus lateralization (Weisz et al., 2007). We compare both groups (left-sided and right-sided) of strictly unilateral tinnitus patients with a control group. Furthermore, region of interest analyses were conducted for the primary auditory cortex, the secondary auditory cortex and the parahippocampal area, both left and right side. We include the parahippocampal area as previous research already suggests the involvement of this area in the generation of tinnitus (De Ridder et al., 2006; Landgrebe et al., 2009). The involvement of the parahippocampus might be related to the constant updating of the tinnitus percept from memory and as such prevent habituation (De Ridder et al., 2006). The parahippocampal area has been considered the gatekeeper to the hippocampus (Tulving and Markowitsch, 1997). Repetitive auditory stimuli both in animals (Bickford et al., 1993) and humans (Boutros et al., 2008) lead to attenuation of evoked potentials, but with differences in hippocampal and parahippocampal areas, as early hippocampal evoked potentials are not attenuated, in accordance with studies performed with single cell recordings (Viskontas et al., 2006). 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 (Diederen et al., 2010). Also connectivity analyses are performed for both groups of unilateral tinnitus patients with a control group.

EXPERIMENTAL PROCEDURES

Participants

Forty-six tinnitus patients (n=46; 24 males and 22 females) with strictly unilateral narrow band noise tinnitus, that is, without tinnitus in the other ear, with a mean age of 52.52 (SD=12.54; range 20–63) were selected from the multidisciplinary Tinnitus Research Initiative (TRI) Clinic of the Antwerp University Hospital, Belgium. The mean tinnitus duration was 5.11 years (SD=7.21; range: 1–25). Twenty-six patients presented with exclusive left-sided tinnitus and 20 patients with exclusive right-sided tinnitus. Individuals with pulsatile tinnitus, Ménière's disease, otosclerosis, chronic headache, neurological disorders such as brain tumors, and individuals being treated for mental disorders were not included in the study in order to obtain a very homogeneous sample.

All patients were investigated for the extent of hearing loss using audiograms. 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 0–10 and a validated Dutch translation of the Tinnitus Questionnaire (TQ) (Meeus et al., 2007) was used to asses tinnitus-related distress. No significant differences were found between tinnitus patients for the tinnitus duration, ages, VAS and the TQ. Gender was equally balanced. No significant differences were found for hearing loss, as measured by the loss in decibels (dB SPL) at the tinnitus frequency. See Table 1 for overview.

EEG data collection

EEGs (Mitsar, Nova Tech EEG, Inc, Mesa) were obtained in a fully lighted room with each participants sitting upright in a comfortable chair. The EEG was sampled with 19 electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, O2) in the standard 10–20 International placement referenced to linked lobes and impedances were checked to remain below 5 kΩ. Data were collected for 100 2-s epochs eyes closed, sampling

Table 1. Patients' characteristics

	Lateralization			
	Left	Right	Control	*P-value*
Sex				
Male	14	10	10	.59
Female	12	10	11	
Age				
M	51.00	53.68	56.33	.19
SD	14.85	10.63	7.61	
Tinnitus duration				
M	5.29	4.85	–	.84
SD	6.49	8.36		
VAS intensity				
M	6.44	5.71	–	.30
SD	2.11	2.93		
TQ				
M	47.94	40.72	–	.49
SD	10.72	17.52		
Hearing loss[a]				
M	30.58	33.75	–	.72
(dB HL)				
SD	15.99	17.74		

[a] Mean HL at the tinnitus frequency.

rate=1024 Hz, and band passed 0.15–200 Hz. Data were resampled to 128 Hz, band-pass filtered (fast Fourier transform filter) to 2–44 Hz. These data were transposed into Eureka! Software (Congedo, 2002), plotted and carefully inspected for manual for artifacts. All episodes containing artifacts including eye blinks, eye movements, teeth clenching, body movement, or electrocardiography artifacts were removed from the stream of the electroencephalography (EEG). In addition, an independent component analysis (ICA) was conducted to further verify if all artifacts were excluded, analogue to Moazami-Goudarzi (Moazami-Goudarzi et al., 2010). We employed the group blind source separation approach consisting of the approximate joint diagonalization of grand-average Fourier co-spectral matrices (Congedo et al., 2010a,b). Such method can separate uncorrelated sources with non-proportional power spectra (Congedo et al., 2008) and is analogous to the averaging group ICA approach described for functional magnetic resonance imaging (fMRI) by Schmithorst and Holland (Schmithorst and Holland, 2004) and for EEG by Congedo et al. (Congedo et al., 2010a,b). To investigate the effect of a possible ICA component rejection, we compared the power spectra in two approaches: (1) after visual artifact rejection only (before ICA) and (2) after additional ICA component rejection (after ICA). To test for significant differences between the two approaches we performed a repeated-measure ANOVA, considering mean band power as within-subject variables and groups (left-sided and right-sided) as between-subject variable. The mean power gamma (30.5–44 Hz) did not show a statistically significant difference between the two approaches ($P>.87$). Therefore, we continue by reporting the results of ICA corrected data.

Control subjects

Similar to the tinnitus patients EEGs (Mitsar, Nova Tech EEG, Inc, Mesa) were obtained for a control group ($n=21$; 11 males and 10 females) in a fully lighted room with each participant sitting upright in a comfortable chair in the same measurement situation. The mean age of the control subjects was 56.33 years (SD=7.61; range: 20–63). The control group was age and gender matched.

Source localization

Standardized low-resolution brain electromagnetic tomography (sLORETA) was used to estimate the intracerebral electrical sources that generated the scalp-recorded activity in the gamma frequency bands (Pascual-Marqui, 2002). sLORETA computes electric neuronal activity as current density (A/m^2) without assuming a predefined number of active sources. The sLORETA solution space consists of 6,239 voxels (voxel size: $5\times5\times5$ mm^3) and is restricted to cortical gray matter and hippocampi, as defined by digitized MNI152 template (Fuchs et al., 2002). Scalp electrode coordinates on the Montreal Neurological Institute (MNI) brain are derived from the international 5% system (Jurcak et al., 2007).

The tomography sLORETA has received considerable validation from studies combining LORETA with other more established localization methods, such as fMRI (Vitacco et al., 2002; Mulert et al., 2004), structural MRI (Worrell et al., 2000), PET (Dierks et al., 2000; Pizzagalli et al., 2004; Zumsteg et al., 2005). Further sLORETA validation has been based on accepting as ground truth the localization findings obtained from invasive, implanted depth electrodes, in which case there are several studies in epilepsy (Zumsteg et al., 2006a,c) and cognitive ERPs (Volpe et al., 2007). It is worth emphasizing that deep structures such as the anterior cingulate cortex (Pizzagalli et al., 2001), and mesial temporal lobes (Zumsteg et al., 2006b) can be correctly localized with these methods. In the current implementation of sLORETA, computations were made in a realistic head model (Fuchs et al., 2002), using the MNI152 template (Mazziotta et al., 2001), with the three-dimensional solution space restricted to cortical gray matter, as determined by the probabilistic Talairach atlas (Lancaster et al., 2000). The standard electrode positions on the MNI152 scalp were taken from (Jurcak et al., 2007) and (Oostenveld and Praamstra, 2001). The intracerebral volume is partitioned in 6239 voxels at 5 mm spatial resolution. Thus, sLORETA images represent the standardized electric activity at each voxel in neuroanatomic MNI space as the exact magnitude of the estimated current density. Anatomical labels as Brodmann areas are also reported using MNI space, with correction to Talairach space (Brett et al., 2002).

Region of interest analysis

The log-transformed electrical current density was averaged across all voxels belonging to the region of interest, for primary auditory cortex (BA41), secondary auditory cortex (BA21, BA22) and the parahippocampus (BA35). This was analyzed for left and right sided tinnitus separately for the gamma (30.5–45 Hz) frequency band.

Functional connectivity

Coherence and 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 (Pascual-Marqui et al., 2011). However, Pascual-Marqui et al. (2011) introduced a new technique (i.e. Hermitian covariance matrices) that removes this confounding factor (Pascual-Marqui et al., 2011). Based on the method this measure of dependence can be applied to any number of brain areas jointly, that is, they reflect a global functional connectivity between all series included in the analysis. 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 and are defined in the gamma (30.5–45 Hz) frequency domain. Based on this principle lagged linear connectivity was calculated. Regions of interest selected were the parahippocampal area (BA35), primary auditory cortex (BA41), secondary auditory cortex (BA21, BA22).

Statistical analyses

In order to identify potential differences in brain electrical activity between conditions, sLORETA was then used to perform voxel-by-voxel between-condition comparisons of the current density distribution (*t*-test). Nonparametric statistical analyses of functional sLORETA images (statistical non-parametric mapping; SnPM) were performed for each contrast employing a t-statistic for paired groups and a corrected ($P<0.05$). As explained by Nichols and Holmes, the SnPM methodology does not require any assumption of Gaussianity and corrects for all multiple comparisons (Nichols and Holmes, 2002). We performed one voxel-by-voxel test (comprising 6,239 voxels each) for the gamma frequency band.

A comparison was made using one-way ANOVA for the respective regions of interest (left primary auditory cortex, right primary auditory cortex, left secondary auditory cortex, right secondary auditory cortex, left parahippocampal area and right parahippocampal area) between left-sided tinnitus patients, right-sided tinnitus patients and a control group. Next, also a repeated measure ANOVA was conducted with the parahippocampal area (left and right) as within-subject variable and tinnitus side (left and right) as between subject variable. Similar analyses were conducted for respectively the primary and secondary auditory cortex.

Connectivity contrast maps were calculated through multiple voxel-by-voxel between-condition comparisons of the current density distribution. Again a comparison was made between the tinnitus group (left-sided tinnitus and right-sided tinnitus, respectively) and control subjects.

Fig. 1. Comparison between a respectively left-sided tinnitus patient with a control group and right-sided tinnitus patient with control group for the gamma-band frequency (30.5–44 Hz). For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

RESULTS

An sLORETA comparison between left and right-sided tinnitus for gamma-band activity revealed no significant differences. A similar analysis comparing left-sided tinnitus patients with a control group revealed however a significant effect ($P<.05$) within the right parahippocampal area. This demonstrated that left-sided tinnitus patients harbored more gamma activity in that area (see Fig. 1, top panel). Also a significant effect was obtained when comparing right-sided tinnitus patients with a control group, indicating that there was more synchronized gamma activity in the left parahippocampal area (see Fig. 1, bottom panel).

A one-way ANOVA revealed that when comparing left-sided tinnitus patients, right-sided tinnitus patients and a control group a significant main effect can be noted for respectively the left primary auditory cortex ($F(2,66)=8.97$, $P<.001$), right primary auditory cortex ($F(2,66)=6.50$, $P<.01$), left secondary auditory cortex ($F(2,66)=5.76$, $P<.01$), right secondary auditory cortex ($F(2,66)=3.38$, $P<.05$), left parahippocampal area ($F(2,66)=3.32$, $P<.05$), and a marginal significance for the right parahippocampal area ($F(2,66)=2.52$, $P<.10$) (see Fig. 2 for overview). A Bonferroni multiple comparison analysis revealed that for left primary auditory cortex, right primary auditory cortex, left secondary auditory cortex, right secondary auditory cortex respectively left-sided tinnitus patients and right-sided tinnitus patients significantly differ from the control group ($P<.05$). Both left-sided tinnitus and right-sided tinnitus patients did not differ from each other for this ROI. However, for the left parahippocampal area, right-sided tinnitus patients significantly differ from respectively left-sided tinnitus patients and the control group ($P<.05$). No difference was found for left-sided parahippocampal activity between left-sided tinnitus patients and the control group. The opposite was found for the right parahippocampal area. Left-sided tinnitus patients significantly differ from respectively right-sided tinnitus patients and the control group ($P<.10$). No difference was found for right parahippocampal activity between right-sided tinnitus patients and the control group.

A repeated measure ANOVA yielded a significant two-way interaction effect between the parahippocampal area (left vs. right) $\times$ tinnitus side (left vs. right), $F(1,44)=5.19$, $P<.05$ (see Fig. 3). Simple contrast analysis indicated that the right parahippocampal area has marginal significantly higher logarithmic current density in comparison to the left parahippocampal area for the left-sided tinnitus ($F(1,44)=2.74$, $P<.05$). Similar analysis revealed also that the left parahippocampal area has a trend with a higher logged current density in comparison to the right parahippocampal area for the right-sided tinnitus ($F(1,44)=2.82$, $P<.05$). No effect could be obtained for the main effect of tinnitus side (left vs.

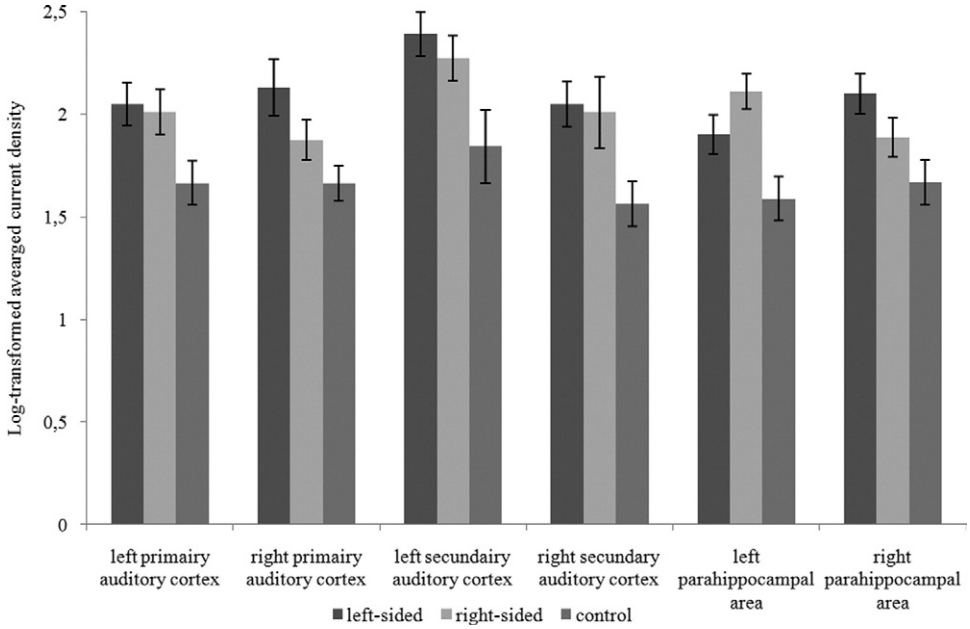

Fig. 2. Logged transformed averaged current density for the gamma-band frequency (30.5–44 Hz) comparing left-sided tinnitus patients, right-sided tinnitus patients and control group showed a significant effect of the left primary auditory cortex ($F(2,66)=8.97$, $P<.001$), the right primary auditory cortex ($F(2,66)=6.50$, $P<.01$), the left secondary auditory cortex ($F(2,66)=5.76$, $P<.01$), the right secondary auditory cortex ($F(2,66)=3.38$, $P<.05$), the left parahippocampal area ($F(2,66)=3.32$, $P<.05$), and a marginal significance for the right parahippocampal area ($F(2,66)=2.52$, $P<.10$).

right) or parahippocampal area (left vs. right). As for the region of interest analyses for primary auditory cortex as well as for the secondary primary auditory cortex no significant main and interaction effects were obtained.

A connectivity analysis between left and right-sided tinnitus for gamma-band activity revealed no significant differences. A connectivity analysis between left-sided tinnitus patients and control subjects demonstrated a significant ($P<.01$; see Fig. 4 and Table 2) increased synchronized gamma connectivity from the right parahippocampal area to the left primary auditory cortex. From the left primary auditory cortex increased gamma synchronized connectivity was found to the right primary auditory and right secondary auditory cortex and from the right secondary auditory cortex to the left secondary auditory cortex.

A connectivity analysis between the right-sided tinnitus patients and control subjects revealed significant ($P<.01$; see Fig. 5 and Table 3) increased synchronized gamma connectivity between the left parahippocampal area to left and right secondary auditory. In addition also a significant connection was found between the right secondary auditory and the left primary auditory cortex and from the left

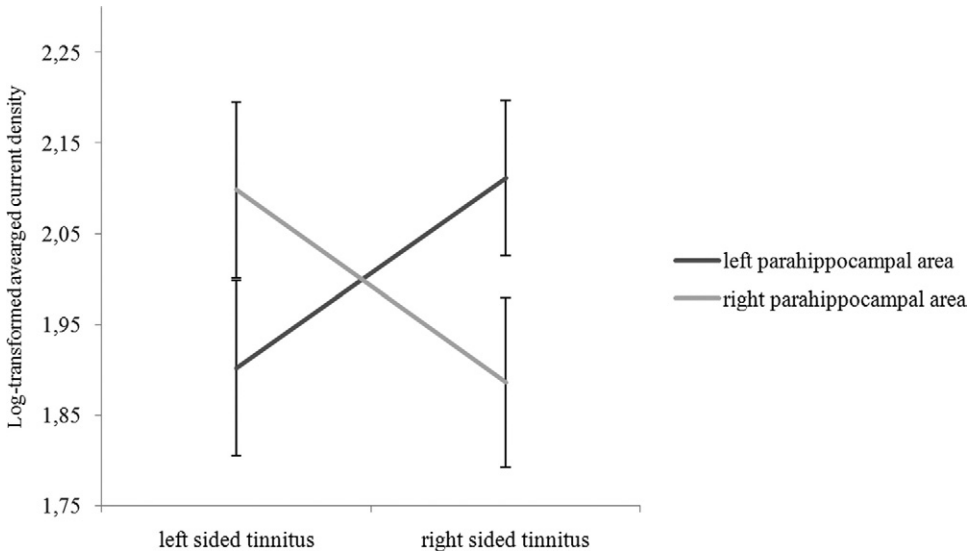

Fig. 3. Significant two-way interaction effect ($F(1,44)=5.19$, $P<.05$) for the logged transformed averaged current density for the gamma-band frequency (30.5–44 Hz) when comparing left with right-sided tinnitus for respectively of the left and right parahippocampal area.

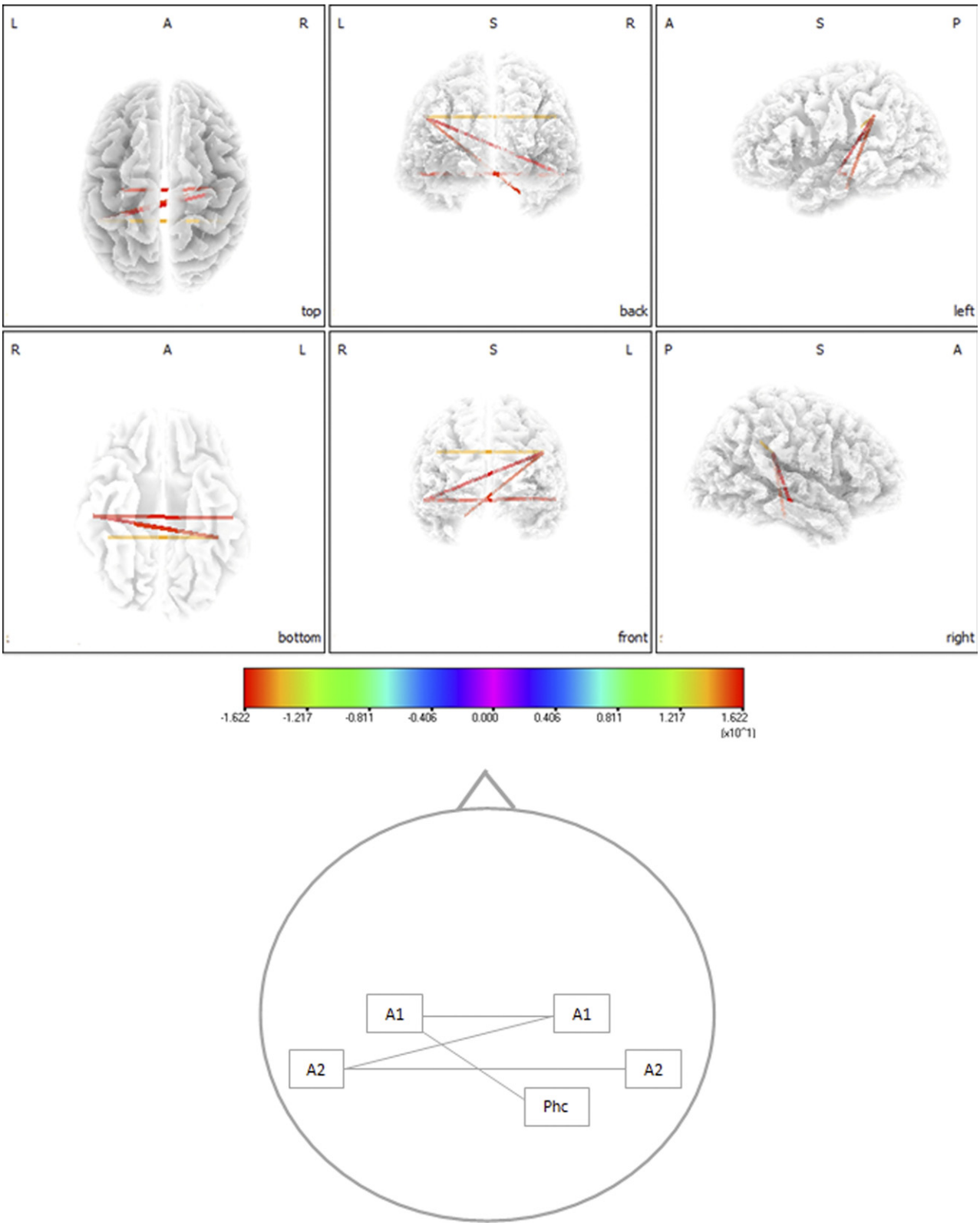

Fig. 4. Significant differences in functional connectivity between left-sided tinnitus patients and control subjects for the gamma-band frequency (30.5–44 Hz). For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

Table 2. Coherence group means for left-sided tinnitus patient vs. control

	A2 left	PHC left	A1 right	A2 right	PHC right
A1 left	11.25	12.86	15.90	7.96	11.13
A2 left		10.54	16.22	14.09	15.59
PHC left			12.86	8.07	10.51
A1 right				10.13	10.74
A2 right					8.07

primary cortex to the right primary auditory cortex for the right-sided tinnitus patients. Also functional connectivity was found between the left and right secondary cortex. Finally increased significant synchronized gamma connectivity was found between the left primary auditory cortex and the right parahippocampal area.

DISCUSSION

The aim of the present study was to detect functional differences in gamma-band activity in resting state EEG for left and right-sided tinnitus patients in order to further explore the discussion on the cerebral lateralization of tinnitus. The most important result of this study is that tinnitus lateralization depended on the parahippocampal area. More precisely, unilateral tinnitus is characterized by more synchronized gamma activity in the contralateral parahippocampal area. As for the auditory cortex no differences were found between left-sided and right-sided tinnitus patients. However, in comparison to the control group both left and right-sided tinnitus patients had an increased gamma-band activity in both the left and right primary and secondary auditory cortex. Connectivity analysis further revealed that the parahippocampal area plays an important role in both left-sided and right-sided tinnitus and has connections with the auditory cortex. It was further revealed that the parahippocampal areas are directly or indirectly connected with the primary and secondary auditory cortex, more so than in control subjects.

While previous research already indicated that there was a difference between bilateral tinnitus and respectively left- and right-sided tinnitus in the parahippocampal area within the gamma frequency band (Vanneste et al., 2011). Our results extend these findings by indicating that there is a lateralization effect within left- and right-sided tinnitus patients for the parahippocampal area. The parahippocampal involvement in tinnitus pathophysiology is demonstrated by histopathologic findings of posterior hippocampus (i.e. parahippocampal area) lesions in patients, who experience tinnitus as a symptom of methyltin intoxications (Rey et al., 1984; Kreyberg et al., 1992). Bilateral hippocampal resection with remaining posterior parahippocampal areas can cause tinnitus, as evidenced by the case of famous amnestic patient H.M. (Corkin et al., 1997). Further electrophysiological studies demonstrated that auditory habituation is disrupted after amygdalohippocampal resections in humans (Hämäläinen et al., 2007). Injecting amibarbital, a short-acting barbiturate, suprase-lectively in the anterior choroidal artery, which supplies the amygdalohippocampal area, contralaterally to the side on which the tinnitus is perceived, can temporarily suppress pure tone tinnitus in some patients (De Ridder et al., 2006) confirming these electrophysiological data.

Our data confirm that the parahippocampal area plays an important role in tinnitus. However our results further suggest that left-sided tinnitus is characterized by high current density activity in the right parahippocampus, while the opposite is present for right-sided tinnitus.

Because there is a direct connection between the parahippocampus and the auditory cortex (Grunwald et al., 2003; Boutros et al., 2005, 2008; Korzyukov et al., 2007), increased gamma activity in the parahippocampus can lead to increased gamma activity in the auditory cortex. This study confirms the involvement of the auditory cortex in tinnitus in accordance with previous functional imaging (Arnold et al., 1996; Langguth et al., 2006a) as well as treatment studies (Eichhammer et al., 2003; De Ridder et al., 2010). Surprisingly, however is that this study does not show any differences in auditory cortex gamma-band activity between left and right-sided tinnitus. Other studies have found that tinnitus intensity seems to correlate with increased gamma-band activity in the contralateral auditory cortex (van der Loo et al., 2009). This study, however, did not look for correlations between gamma-band activity and the perceived intensity of the phantom sound. MEG data found increased gamma in the auditory cortex in tinnitus patients in comparison to a control group (Weisz et al., 2007), a result confirmed in this EEG study. Yet the laterality index at 55 Hz observed in the MEG study was not computed here as the EEG was filtered to 45 Hz, analyzing only low frequency gamma-band activity. Our findings further reveal that respectively left and right parahippocampal areas are connected to the left and right auditory cortex and the left and right auditory cortex are have more synchronized gamma connectivity in tinnitus patients. That is, for left-sided tinnitus patients the right parahippocampal area has increased synchronized gamma connectivity with the right auditory cortex and for right-sided tinnitus patients an increased synchronized gamma connectivity with the left auditory cortex was found. However for the right-sided tinnitus patients also increased synchronized gamma connectivity was found between the right parahippocampal area and the left auditory cortex.

It is unclear why no differential activity is found in the auditory cortex. One potential explanation could be that other forms of tinnitus (e.g. pure tone tinnitus) may be accompanied by changes in the auditory cortex. Recent findings also suggest that the involvement of the auditory cortex in the pathophysiology of tinnitus decreases with increasing tinnitus duration (De Ridder et al., 2005; Kleinjung et al., 2007; Schlee et al., 2009), and the average tinnitus duration of the patient population studied was 4.68 years, that is, after 4 years, when auditory cortex involvement changes (Schlee et al., 2009). It is also possible that high frequency gamma-band activity (>45 Hz) lateralizes in contrast to low frequency gamma-band activity, analogous to MEG data (Weisz et al., 2007), or that only gamma nested on theta lateralizes (Weisz et al., 2007).

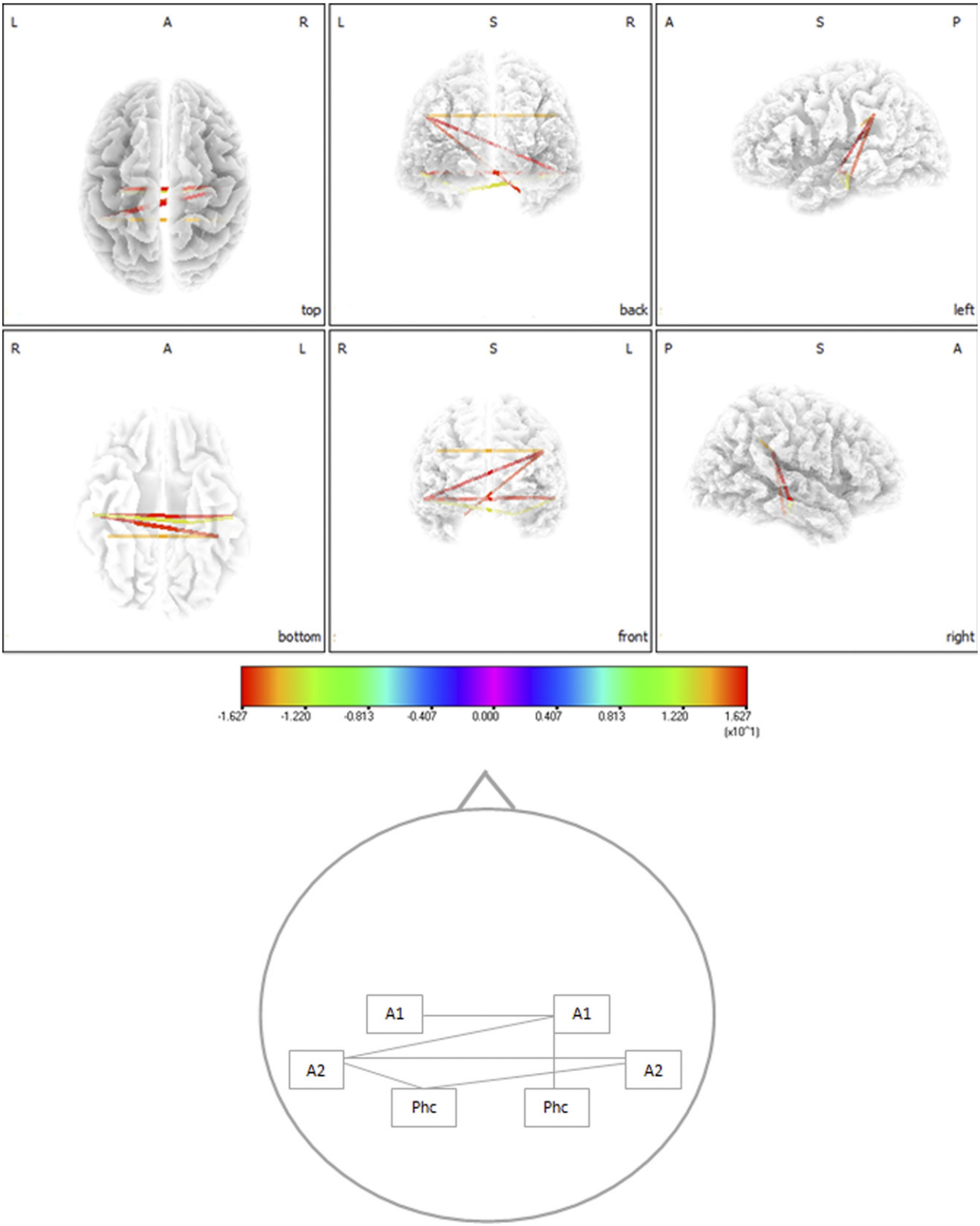

Fig. 5. Significant differences in functional connectivity between right-sided tinnitus patients and control subjects for the gamma-band frequency (30.5–44 Hz). For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

Table 3. Coherence group means for right-sided tinnitus patient vs. control

	A2 left	PHC left	A1 right	A2 right	PHC right
A1 left	11.24	12.94	15.92	8.00	11.16
A2 left		10.54	16.27	14.12	15.61
PHC left			12.94	8.16	10.56
A1 right				10.13	10.82
A2 right					8.16

Although our results give a good indication between the difference in left-sided and right-sided tinnitus, the method applied make use of a low-resolution brain tomography. Deep sources located in the limbic system and thalamic areas are not possible to detect with source localized EEG. Other neuroimaging techniques such as high-resolution fMRI are necessary to further explore these deep structures.

In conclusion, our results reveal that the parahippocampus is important in the lateralization of noise-like tinnitus. Further efforts should be made to better understand the role of the parahippocampus and in extension the role of the limbic system, in the circuit of brain areas related to auditory phantom perception.

REFERENCES

Andersson G, Lyttkens L, Hirvelä C, Furmark T, Tillfors M, Fredrikson M (2000) Regional cerebral blood flow during tinnitus: a PET case study with lidocaine and auditory stimulation. Acta Otolaryngol 120:967–972.

Arnold W, Bartenstein P, Oestreicher E, Romer W, Schwaiger M (1996) Focal metabolic activation in the predominant left auditory cortex in patients suffering from tinnitus: a PET study with [18F]deoxyglucose. ORL J Otorhinolaryngol Relat Spec 58:195–199.

Ashton H, Reid K, Marsh R, Johnson I, Alter K, Griffiths T (2007) High frequency localised "hot spots" in temporal lobes of patients with intractable tinnitus: a quantitative electroencephalographic (QEEG) study. Neurosci Lett 426:23–28.

Axelsson A, Ringdahl A (1989) Tinnitus—a study of its prevalence and characteristics. Br J Audiol 23:53–62.

Bickford PC, Luntz-Leybman V, Freedman R (1993) Auditory sensory gating in the rat hippocampus: modulation by brainstem activity. Brain Res 607:33–38.

Boutros NN, Mears R, Pflieger ME, Moxon KA, Ludowig E, Rosburg T (2008) Sensory gating in the human hippocampal and rhinal regions: regional differences. Hippocampus 18:310–316.

Boutros NN, Trautner P, Rosburg T, Korzyukov O, Grunwald T, Schaller C, Elger CE, Kurthen M (2005) Sensory gating in the human hippocampal and rhinal regions. Clin Neurophysiol 116: 1967–1974.

Brett M, Johnsrude IS, Owen AM (2002) The problem of functional localization in the human brain. Nat Rev Neurosci 3:243–249.

Congedo M (2002) EureKa! (Version 3.0) [Computer Software]. Knoxville, TN: NovaTech EEG Inc. Freeware available at www.NovaTechEEG.

Congedo M, Gouy-Pailler C, Jutten C (2008) On the blind source separation of human electroencephalogram by approximate joint diagonalization of second order statistics. Clin Neurophysiol 119:2677–2686.

Congedo M, John RE, De Ridder D, Prichep L (2010a) Group independent component analysis of resting state EEG in large normative samples. Int J Psychophysiol 78:89–99.

Congedo M, John RE, De Ridder D, Prichep L, Isenhart R (2010b) On the "dependence" of "independent" group EEG sources; an EEG study on two large databases. Brain Topogr 23:134–138.

Corkin S, Amaral DG, González RG, Johnson KA, Hyman BT (1997) H. M.'s medial temporal lobe lesion: findings from magnetic resonance imaging. J Neurosci 17:3964–3979.

De Ridder D (2010) Should rTMS for tinnitus be performed left-sided, ipsilaterally or contralaterally, and is it a treatment or merely investigational? Eur J Neurol 17:891–892.

De Ridder D, Fransen H, Francois O, Sunaert S, Kovacs S, Van De Heyning P (2006) Amygdalohippocampal involvement in tinnitus and auditory memory. Acta Otolaryngol Suppl: 50–53.

De Ridder D, van der Loo E, Van der Kelen K, Menovsky T, van de Heyning P, Moller A (2007) Theta, alpha and beta burst transcranial magnetic stimulation: brain modulation in tinnitus. Int J Med Sci 4:237–241.

De Ridder D, Vanneste S, van der Loo E, Plazier M, Menovsky T, van de Heyning P (2010) Burst stimulation of the auditory cortex: a new form of neurostimulation for noise-like tinnitus suppression. J Neurosurg 112:1289–1294.

De Ridder D, Verstraeten E, Van der Kelen K, De Mulder G, Sunaert S, Verlooy J, Van de Heyning P, Moller A (2005) Transcranial magnetic stimulation for tinnitus: influence of tinnitus duration on stimulation parameter choice and maximal tinnitus suppression. Otol Neurotol 26:616–619.

Diederen KM, Neggers SF, Daalman K, Blom JD, Goekoop R, Kahn RS, Sommer IE (2010) Deactivation of the parahippocampal gyrus preceding auditory hallucinations in schizophrenia. Am J Psychiatry 167:427–435.

Dierks T, Jelic V, Pascual-Marqui RD, Wahlund L, Julin P, Linden DE, Maurer K, Winblad B, Nordberg A (2000) Spatial pattern of cerebral glucose metabolism (PET) correlates with localization of intracerebral EEG-generators in Alzheimer's disease. Clin Neurophysiol 111:1817–1824.

Eichhammer P, Hajak G, Kleinjung T, Landgrebe M, Langguth B (2007) Functional imaging of chronic tinnitus: the use of positron emission tomography. Prog Brain Res 166:83–88.

Eichhammer P, Langguth B, Marienhagen J, Kleinjung T, Hajak G (2003) Neuronavigated repetitive transcranial magnetic stimulation in patients with tinnitus: a short case series. Biol Psychiatry 54: 862–865.

Fuchs M, Kastner J, Wagner M, Hawes S, Ebersole JS (2002) A standardized boundary element method volume conductor model. Clin Neurophysiol 113:702–712.

Grunwald T, Boutros NN, Pezer N, von Oertzen J, Fernández G, Schaller C, Elger CE (2003) Neuronal substrates of sensory gating within the human brain. Biol Psychiatry 53:511–519.

Hämäläinen H, Kujala T, Kekoni J, Hurskainen H, Pirilä J, Wikström H, Huotilainen M (2007) Effects of unilateral hippocampus-amygdala-partial temporal lobe resection on auditory EEG/MEG responses: a case study. Scand J Psychol 48:367–373.

Heller AJ (2003) Classification and epidemiology of tinnitus. Otolaryngol Clin North Am 36:239–248.

Joliot M, Ribary U, Llinás R (1994) Human oscillatory brain activity near 40 Hz coexists with cognitive temporal binding. Proc Natl Acad Sci U S A 91:11748–11751.

Jurcak V, Tsuzuki D, Dan I (2007) 10/20, 10/10, and 10/5 systems revisited: their validity as relative head-surface-based positioning systems. Neuroimage 34:1600–1611.

Khedr EM, Abo-Elfetoh N, Rothwell JC, El-Atar A, Sayed E, Khalifa H (2010) Contralateral versus ipsilateral rTMS of temporoparietal cortex for the treatment of chronic unilateral tinnitus: comparative study. Eur J Neurol 17:976–983.

Kleinjung T, Steffens T, Sand P, Murthum T, Hajak G, Strutz J, Langguth B, Eichhammer P (2007) Which tinnitus patients benefit from transcranial magnetic stimulation? Otolaryngol Head Neck Surg 137:589–595.

Kleinjung T, Vielsmeier V, Landgrebe M, Hajak G, Langguth B (2008) Transcranial magnetic stimulation: a new diagnostic and therapeutic tool for tinnitus patients. Int Tinnitus J 14:112–118.

Korzyukov O, Pflieger ME, Wagner M, Bowyer SM, Rosburg T, Sundaresan K, Elger CE, Boutros NN (2007) Generators of the intracranial P50 response in auditory sensory gating. Neuroimage 35:814–826.

Kreyberg S, Torvik A, Bjørneboe A, Wiik-Larsen W, Jacobsen D (1992) Trimethyltin poisoning: report of a case with postmortem examination. Clin Neuropathol 11:256–259.

Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, Rainey L, Kochunov PV, Nickerson D, Mikiten SA, Fox PT (2000) Automated Talairach Atlas labels for functional brain mapping. Hum Brain Mapp 10:120–131.

Landgrebe M, Langguth B, Rosengarth K, Braun S, Koch A, Kleinjung T, May A, de Ridder D, Hajak G (2009) Structural brain changes in tinnitus: grey matter decrease in auditory and non-auditory brain areas. Neuroimage 46:213–218.

Langguth B, Eichhammer P, Kreutzer A, Maenner P, Marienhagen J, Kleinjung T, Sand P, Hajak G (2006a) The impact of auditory cortex activity on characterizing and treating patients with chronic tinnitus—first results from a PET study. Acta Otolaryngol Suppl: 84–88.

Langguth B, Zowe M, Landgrebe M, Sand P, Kleinjung T, Binder H, Hajak G, Eichhammer P (2006b) Transcranial magnetic stimulation for the treatment of tinnitus: a new coil positioning method and first results. Brain Topogr 18:241–247.

Llinás R, Urbano FJ, Leznik E, Ramírez RR, van Marle HJ (2005) Rhythmic and dysrhythmic thalamocortical dynamics: GABA systems and the edge effect. Trends Neurosci 28:325–333.

Llinás RR, Ribary U, Jeanmonod D, Kronberg E, Mitra PP (1999) Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. Proc Natl Acad Sci U S A 96:15222–15227.

Mazziotta J, Toga A, Evans A, Fox P, Lancaster J, Zilles K, Woods R, Paus T, Simpson G, Pike B, Holmes C, Collins L, Thompson P, MacDonald D, Iacoboni M, Schormann T, Amunts K, Palomero-Gallagher N, Geyer S, Parsons L, Narr K, Kabani N, Le Goualher G, Boomsma D, Cannon T, Kawashima R, Mazoyer B (2001) A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM) Philos Trans R Soc Lond B Biol Sci 356:1293–1322.

Meeus O, Blaivie C, Van de Heyning P (2007) Validation of the Dutch and the French version of the Tinnitus Questionnaire. B-ENT 3(Suppl 7):11–17.

Melcher JR, Sigalovsky IS, Guinan JJ Jr., Levine RA (2000) Lateralized tinnitus studied with functional magnetic resonance imaging: abnormal inferior colliculus activation. J Neurophysiol 83:1058–1072.

Moazami-Goudarzi M, Michels L, Weisz N, Jeanmonod D (2010) Temporo-insular enhancement of EEG low and high frequencies in patients with chronic tinnitus. QEEG study of chronic tinnitus patients. BMC Neurosci 11:40.

Møller AR (2007) Tinnitus: presence and future. Prog Brain Res 166:3–16.

Mühlnickel W, Elbert T, Taub E, Flor H (1998) Reorganization of auditory cortex in tinnitus. Proc Natl Acad Sci U S A 95:10340–10343.

Mulert C, Jäger L, Schmitt R, Bussfeld P, Pogarell O, Möller HJ, Juckel G, Hegerl U (2004) Integration of fMRI and simultaneous EEG: towards a comprehensive understanding of localization and time-course of brain activity in target detection. Neuroimage 22:83–94.

Nichols TE, Holmes AP (2002) Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum Brain Mapp 15:1–25.

Oostenveld R, Praamstra P (2001) The five percent electrode system for high-resolution EEG and ERP measurements. Clin Neurophysiol 112:713–719.

Pascual-Marqui RD (2002) Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. Methods Find Exp Clin Pharmacol 24(Suppl D):5–12.

Pascual-Marqui RD, Lehmann D, Koukkou M, Kochi K, Anderer P, Saletu B, Tanaka H, Hirata K, John ER, Prichep L, Biscay-Lirio R, Kinoshita T (2011) Assessing interactions in the brain with exact low-resolution electromagnetic tomography. Philos Transact A Math Phys Eng Sci 369:3768–3784.

Pizzagalli D, Pascual-Marqui RD, Nitschke JB, Oakes TR, Larson CL, Abercrombie HC, Schaefer SM, Koger JV, Benca RM, Davidson RJ (2001) Anterior cingulate activity as a predictor of degree of treatment response in major depression: evidence from brain electrical tomography analysis. Am J Psychiatry 158:405–415.

Pizzagalli DA, Oakes TR, Fox AS, Chung MK, Larson CL, Abercrombie HC, Schaefer SM, Benca RM, Davidson RJ (2004) Functional but not structural subgenual prefrontal cortex abnormalities in melancholia. Mol Psychiatry 9:325, 393–405.

Rey C, Reinecke HJ, Besser R (1984) Methyltin intoxication in six men; toxicologic and clinical aspects. Vet Hum Toxicol 26:121–122.

Schlee W, Hartmann T, Langguth B, Weisz N (2009) Abnormal resting-state cortical coupling in chronic tinnitus. BMC Neurosci 10:11.

Schmithorst VJ, Holland SK (2004) Comparison of three methods for generating group statistical inferences from independent component analysis of functional magnetic resonance imaging data. J Magn Reson Imaging 19:365–368.

Smits M, Kovacs S, de Ridder D, Peeters RR, van Hecke P, Sunaert S (2007) Lateralization of functional magnetic resonance imaging (fMRI) activation in the auditory pathway of patients with lateralized tinnitus. Neuroradiology 49:669–679.

Steriade M (2006) Grouping of brain rhythms in corticothalamic systems. Neuroscience 137:1087–1106.

Tulving E, Markowitsch HJ (1997) Memory beyond the hippocampus. Curr Opin Neurobiol 7:209–216.

van der Loo E, Gais S, Congedo M, Vanneste S, Plazier M, Menovsky T, Van de Heyning P, De Ridder D (2009) Tinnitus intensity dependent gamma oscillations of the contralateral auditory cortex. PLoS One 4:e7396.

Vanneste S, Plazier M, van der Loo E, Van de Heyning P, De Ridder D (2011) The difference between uni- and bilateral auditory phantom percept. Clin Neurophysiol 122:578–587.

Viskontas IV, Knowlton BJ, Steinmetz PN, Fried I (2006) Differences in mnemonic processing by neurons in the human hippocampus and parahippocampal regions. J Cogn Neurosci 18:1654–1662.

Vitacco D, Brandeis D, Pascual-Marqui R, Martin E (2002) Correspondence of event-related potential tomography and functional magnetic resonance imaging during language processing. Hum Brain Mapp 17:4–12.

Volpe U, Mucci A, Bucci P, Merlotti E, Galderisi S, Maj M (2007) The cortical generators of P3a and P3b: a LORETA study. Brain Res Bull 73:220–230.

Weisz N, Müller S, Schlee W, Dohrmann K, Hartmann T, Elbert T (2007) The neural code of auditory phantom perception. J Neurosci 27:1479–1484.

Worrell GA, Lagerlund TD, Sharbrough FW, Brinkmann BH, Busacker NE, Cicora KM, O'Brien TJ (2000) Localization of the epileptic focus by low-resolution electromagnetic tomography in patients with a lesion demonstrated by MRI. Brain Topogr 12:273–282.

Zumsteg D, Lozano AM, Wennberg RA (2006a) Depth electrode recorded cerebral responses with deep brain stimulation of the anterior thalamus for epilepsy. Clin Neurophysiol 117:1602–1609.

Zumsteg D, Lozano AM, Wennberg RA (2006b) Mesial temporal inhibition in a patient with deep brain stimulation of the anterior thalamus for epilepsy. Epilepsia 47:1958–1962.

Zumsteg D, Lozano AM, Wieser HG, Wennberg RA (2006c) Cortical activation with deep brain stimulation of the anterior thalamus for epilepsy. Clin Neurophysiol 117:192–207.

Zumsteg D, Wennberg RA, Treyer V, Buck A, Wieser HG (2005) H2(15)O or 13NH3 PET and electromagnetic tomography (LORETA) during partial status epilepticus. Neurology 65:1657–1660.

(Accepted 27 July 2011)
(Available online 30 August 2011)