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The difference between uni- and bilateral auditory phantom percept

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ABSTRACT

Objective: Tinnitus can be considered an auditory phantom percept, in which patients hear an internal sound in the absence of any external sound source, mimicking tonal memory. Tinnitus however can be perceived exclusively uni- or bilaterally.
Methods: The neurophysiological differences were investigated between unilateral and bilateral tinnitus using LORETA source localized resting state EEG recordings.
Results: The difference between unilateral and bilateral tinnitus is reflected by high frequency activity (beta and gamma) in the superior prefrontal gurus, right parahippocampus, right angular gyrus and right auditory cortex. Unilateral tinnitus is characterized by contralateral beta2 in the superior prefrontal gyrus in comparison to bilateral tinnitus, but gamma in comparison to non-tinnitus subjects. Bilateral tinnitus has delta activity in the ventrolateral prefrontal cortex in comparison to unilateral tinnitus, and bilateral beta1 in comparison to non-tinnitus subjects. Bilateral tinnitus is also characterized by bilateral frontopolar beta1 activity.
Conclusions: Unilateral and bilateral tinnitus can be differentiated based on their resting state oscillation patterns: beta3 and gamma-band activity in the superior premotor cortex, parahippocampal area and angular gyrus seem to form the core of a spatial localization network involved in tinnitus.
Significance: These differences should be taken into account when evaluating functional neuroimaging data relating to tinnitus.

1. Introduction

Tinnitus is an auditory phantom percept, where patients hear an internal sound in the absence of any external sound source. In the population 10–15% experience tinnitus chronically and about 6–25% of the affected people report interference with their lives, as tinnitus causes a considerable amount of distress (Axelsson and Ringdahl, 1989; Baguley, 2002; Eggermont and Roberts, 2004; Heller, 2003). Typically, pain, concentration problems, depression, anxiety, irritability, sleep disturbances, and intense worrying are perceived to be significantly more severe within tinnitus patients (Erlandsson and Holgers, 2001). Hence, this phantom sound can be extremely disruptive and debilitating leading many patients to seek medical attention.

In daily situations, an external sound is perceived bilaterally (Mayer et al., 2009; Wang et al., 2009). In contrast, tinnitus, which is an internal sound, can be experienced exclusively uni- or bilaterally. Previous research reported bilateral tinnitus in 52% of patients (Chermak and Dengerink, 1987). When hearing loss is more severe in the right ear, there is right-sided tinnitus and, when hearing loss is more pronounced in the left ear, the tinnitus is bilateral or more pronounced on the right (Cahani et al., 1984; Nageris et al., 2010). However, phantom pain which can be considered the somatosensory analogue for tinnitus (De Ridder et al., 2007; Moller, 2000; Tonndorf, 1987) is usually perceived unilaterally (Flor et al., 1995; Lockwood et al., 1999). No study to date has looked into the neurophysiological differences between unilateral and bilateral tinnitus, although this could lead to a better understanding of the pathophysiology of tinnitus. Hence, it might be interesting to further explore the perceived spatial localization in tinnitus.

Tinnitus is correlated to gamma-band activity in the auditory cortex (Llinas et al., 1999; van der Loo et al., 2009; Weisz et al., 2007) contralaterally to where the unilateral tinnitus is perceived (Giraud et al., 1999; Lockwood et al., 1998; Smits et al., 2007; van der Loo et al., 2009; Weisz et al., 2007). Bilateral tinnitus could be correlated to bilateral activation in the auditory cortex, similar to perceiving an external sound which usually also evokes bilateral gamma-band activity in the auditory cortex (Pantev et al.,

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1991a,b). In contrast, other researchers claim that tinnitus is typically generated in the left auditory cortex, irrespective how tinnitus is perceived (Andersson et al., 2000; Arnold et al., 1996; Schlee et al., 2009).

New insights into the neurobiology of tinnitus suggest that neuronal changes are not limited to the classical auditory pathways. In particular the dorsolateral prefrontal cortex (Alain et al., 1998; Knight et al., 1989; Lewis et al., 2000; Voisin et al., 2006), anterior cingulate cortex (Mirz et al., 2000; Muhlau et al., 2006; Vanneste et al., 2010), and (para)hippocampus (De Ridder et al., 2006; Landgrebe et al., 2009; Vanneste et al., 2010) seem to be involved in tinnitus too, and it has recently been investigated how these areas coactivate (Schlee et al., 2009). Non-auditory brain areas might be important for the difference between unilateral and bilateral tinnitus as well.

The objective of the present study was to verify the neurophysiological differences between unilateral and bilateral in a homogenous but large group of tinnitus patients using source localized resting state EEG recordings.

2. Methods and materials

2.1. Participants

Sixty-two patients ($N = 62$; 30 males and 32 females) with strictly narrow band noise tinnitus with a mean age of 54.43 were selected from the multidisciplinary Tinnitus Research Initiative (TRI) Clinic of the University Hospital of Antwerp, Belgium. Patients were selected based on their tinnitus lateralization. All patients had tinnitus for more than 1 year and perceive this continuously. Individuals with pulsatile tinnitus, Ménière 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. Patients with CNS-acting medication were excluded as well. In total 35 unilateral tinnitus patients (20 left-sided and 15 right-sided tinnitus patients) and 27 bilateral tinnitus patients were included in the study.

All patients were investigated for the extent of hearing loss using audiograms. Tinnitus matching was performed looking for tinnitus pitch (frequency) and tinnitus intensity. 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 and a validated Dutch translation of the Tinnitus Questionnaire (Meeus et al., 2007) was used to asses tinnitus related distress. No significant differences were found between recent onset and chronic tinnitus patients for the Ages, VAS, and the TQ. Gender was equally balanced. See Table 1 for overview. No significant differences were found for hearing loss, as measured by the loss in decibels (dB SPL) at the tinnitus frequency as well as in the overall hearing loss ($p = .58$). All patients were right handed.

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

Table 1
Patient characteristics and mean and standard deviations for different tinnitus characteristics.

	Tinnitus laterality	
	Unilateral	Bilateral
Gender		
Male	15	15
Female	16	16
Age	54.61(10.95)	54.25(11.45)
Tinnitus duration	4.87(1.03)	4.43(1.25)
VAS intensity	6.45(1.09)	6.78(.89)
TQ	53.51(10.43)	54.68(9.45)

2.2. 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 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 ECG artifacts were removed from the stream of the EEG. In addition, an independent component analysis (ICA) was conducted to further verify if all artifacts were excluded. To investigate the effect 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 (unilateral versus bilateral tinnitus) as between-subject variable. The mean power in delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz) and gamma (30.5–45 Hz) did not show a statistically significant difference between the two approaches. Therefore, we continue by reporting the results of ICA corrected data.

Average cross-spectral matrices were computed for bands delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz) and gamma (30.5–45 Hz).

2.3. NTE normative database

Also the normative database of the Nova Tech EEG (NTE), Inc., Mesa, AZ ($N = 30$; range: 20–30 years) was used (http://www.novatecheeg.com/). None of these subjects were known to suffer from tinnitus or hearing loss. Exclusion criteria for the NTE database were known psychiatric or neurological illness, psychiatric history of drug/alcohol abuse in a participant or any relative, current psychotropic/CNS active medications, history of head injury (with loss of consciousness) or seizures, headache, physical disability. To build the database about 3–5 min of EEG was continuously recorded while participant sat with the eyes closed. EEG data were acquired at the 19 standard leads prescribed by the 10–20 international system (FP1, FP2, F7, F3, FZ, F4, F8, T3, C3, CZ, C4, T4, T5, P3, PZ, P4, T6, O1, O2) using both earlobes as reference and enabling a 60 Hz notch filter to suppress power line contamination. The resistance of all electrodes was kept below 5 kΩ. Data of the NTE database were acquired using the 12-bit A/D NeuroSearch-24 acquisition system (Lexicor Medical Technology, Inc., Boulder, CO) and sampled at 128. In the database all biological, instrumental and environmental artifacts had been removed.

2.4. Source localization

Standardized low-resolution brain electromagnetic tomography (sLORETA) was used to estimate the intracerebral electrical sources

that generated the scalp-recorded activity in each of the eight 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 6239 voxels (voxel size: $5 \times 5 \times 5$ mm) and is restricted to cortical gray matter and hippocampi, as defined by digitized MNI152 template (Fuchs et al., 2002). Scalp electrode coordinates on the MNI brain are derived from the international 10/20 system (Jurcak et al., 2007).

2.5. 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. Non-parametric statistical analyses of functional sLORETA images (statistical non-parametric mapping; SnPM) were performed for each contrast employing a *t*-statistic for unpaired groups and a 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 (Nichols and Holmes, 2002). We performed one voxel-by-voxel test (comprising 6239 voxels each) for the difference frequency bands.

2.6. Region of interest analysis

The log-transformed electric current density was averaged across all voxels belonging to the region of interest, respectively, left and right primary auditory cortex (BA40 and BA41) and left and right secondary auditory cortex (BA21 and BA22) separately for the gamma frequency band.

A multivariate ANOVA (i.e. Wilks' Lambda) for the frequency bands was used with the respective region of interest (i.e. left and right primary auditory cortex (BA40 and BA41) and left and right secondary auditory cortex (BA21 and BA22) as dependent variables and different groups (pure tone, narrow band noise and control subjects) as independent variable. A Bonferroni correction was applied for multiple comparisons.

3. Results

3.1. Unilateral versus bilateral tinnitus

sLORETA yielded significant differences between unilateral and bilateral tinnitus patients ($p < .05$) (see Fig. 1). Increased activity was revealed in the left inferior ventrolateral prefrontal cortex (LFG; BA47) for delta, and the parahippocampus (PHC; BA37), angular gyrus (BA39) and the auditory cortex area (sAC; BA22) for both beta3 and gamma for unilateral tinnitus patients in comparison to bilateral tinnitus patients. In addition, we found decreased activity within beta2 in the right superior premotor cortex (rMMC; BA6 and BA8) for unilateral tinnitus patients in comparison to bilateral tinnitus patients. No significant effect was found for theta, alpha1, alpha2, and beta1.

3.2. Unilateral tinnitus versus NTE normative database (controls)

A sLORETA contrast analysis between unilateral versus NTE normative database demonstrated significantly ($p < .05$) increased activity within gamma (30.5–32 Hz) in the right superior premotor cortex (rMMC; BA8) for unilateral tinnitus patients in comparison to the normative database (see Fig. 2). No significant effects were found for delta, theta, alpha1, alpha2, beta1, beta2 and beta3.

3.3. Bilateral tinnitus versus NTE normative database (controls)

A contrast analysis based on sLORETA between bilateral tinnitus versus NTE normative database showed a significantly ($p < .05$) increased activity within beta1 (13–18 Hz) in the ventrolateral prefrontal cortex extending to frontopolar (LFG; BA47 and BA10) and increased activity within gamma (30.5–32 Hz) in the superior premotor cortex (rMMC; BA8) for bilateral tinnitus patients in comparison to normative database (see Fig. 3). No significant effects were found for delta, theta, alpha1, alpha2, beta2 and beta3.

3.4. Region of interest analysis

A significant effect was found for the log-transformed current density for the different groups on the region of interest (auditory cortex Brodman areas) for the gamma frequency band, $F(16, 164) = 4.30$, $p < .001$ (see Fig. 4). Univariate ANOVA further yielded a significant effect for, respectively, left BA 21 ($F(2, 89) = 10.93$, $p < .001$), left BA 22 ($F(2, 89) = 11.15$, $p < .001$), left BA 40 ($F(2, 89) = 23.93$, $p < .001$), left BA 41 ($F(2, 89) = 11.94$, $p < .001$), right BA 21 ($F(2,<89) = 5.76$, $p < .001$), right BA 22 ($F(2, 89) = 10.78$, $p < .001$), right BA 40 ($F(2, 89) = 12.87$, $p < .001$), and right BA 41 ($F(2, 89) = 6.41$, $p < .001$), A Bonferroni multiple comparison analysis ($p < .05$) revealed that the control subjects had significant lower log averaged current density in comparison to unilateral and bilateral tinnitus patients. Unilateral and bilateral tinnitus patient did not differ from each other, expect for BA22 right. For this latter brain area it was revealed that unilateral tinnitus had higher current densities than bilateral tinnitus patient ($p = .05$).

3.5. Left-sided versus bilateral tinnitus

sLORETA yielded significant differences between left and bilateral tinnitus patient ($p < .05$) (see Fig. 5). Increased activity was revealed in the parahippocampus (PHC; BA37), angular gyrus (BA39) for both beta3 and gamma for left-sided tinnitus patients in comparison to bilateral tinnitus patients. In addition, we found decreased activity within beta2 (18.5–21 Hz) in the right superior premotor cortex (rMMC; BA6 and BA8) for left-sided tinnitus patients in comparison to bilateral tinnitus patients. No significant effects were found for delta, theta, alpha1, alpha2, and beta1.

3.6. Right-sided versus bilateral tinnitus

Significant differences were demonstrated between right-sided and bilateral tinnitus patient ($p < .05$) (see Fig. 6). Decreased activity was revealed within beta2 (18.5–21 Hz) in the right superior premotor cortex (rMMC; BA6 and BA8) for right-sided tinnitus patients in comparison to bilateral tinnitus patients. Furthermore, increased activity was revealed in the parahippocampus (PHC; BA37) and angular gyrus (BA39) for both beta3 for unilateral tinnitus patients in comparison to bilateral tinnitus patients. No significant effects were found for delta, theta, alpha1, alpha2, and beta1, and gamma.

3.7. Frequency analysis of alpha rhythms

To determine whether the differences found might be the result of discrepancies of the individual alpha frequency (IAF) peaks between individuals within the distinct groups (i.e. narrow band noise, pure tone and control) we identified the IAF peak according to literature guidelines (Klimesch, 1996; Klimesch et al., 1998, 1999). This individual alpha frequency peak was defined as the

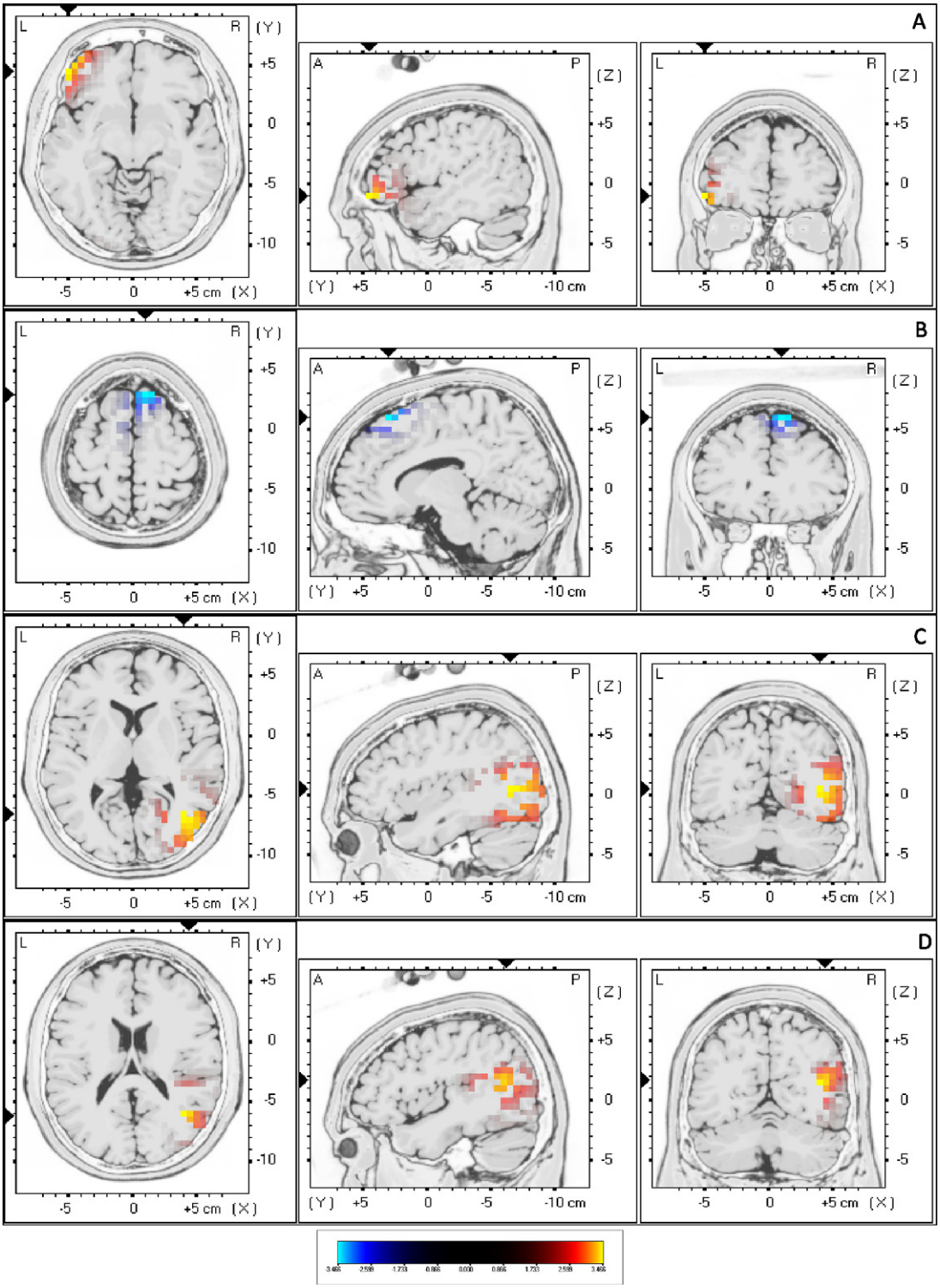

Fig. 1. sLORETA contrast analysis between unilateral versus bilateral tinnitus ($p < .05$): (a) increased delta (1–3.5 Hz) activity in the left inferior ventrolateral prefrontal cortex (LFG; BA47), (B) decreased beta2 (18.5–21 Hz) activity in the right superior premotor cortex (rMMC; BA6 and BA8), and (C and D) increased beta3 (21.5–30 Hz) and gamma (30.5–45 Hz) activity in, respectively, parahippocampal area (PHC; BA37) auditory cortex area (sAC; BA22) and the angular gyrus (BA39).

frequency within the range of 6–13 Hz range of the EEG spectrum showing maximum power. The mean individual alpha frequency was 10.74, 10.53 and 10.95 Hz for, respectively, unilateral tinnitus patients, bilateral patients and control subjects. There was no significant inter-groups difference in the IAF peak as evaluated by an ANOVA ($p > .45$).

4. Discussion

The main objective was to characterize the neurophysiological differences in unilateral versus bilateral tinnitus. Differences were demonstrated with increased synchronized activity in the ventrolateral prefrontal cortex and decreased synchronized activity in

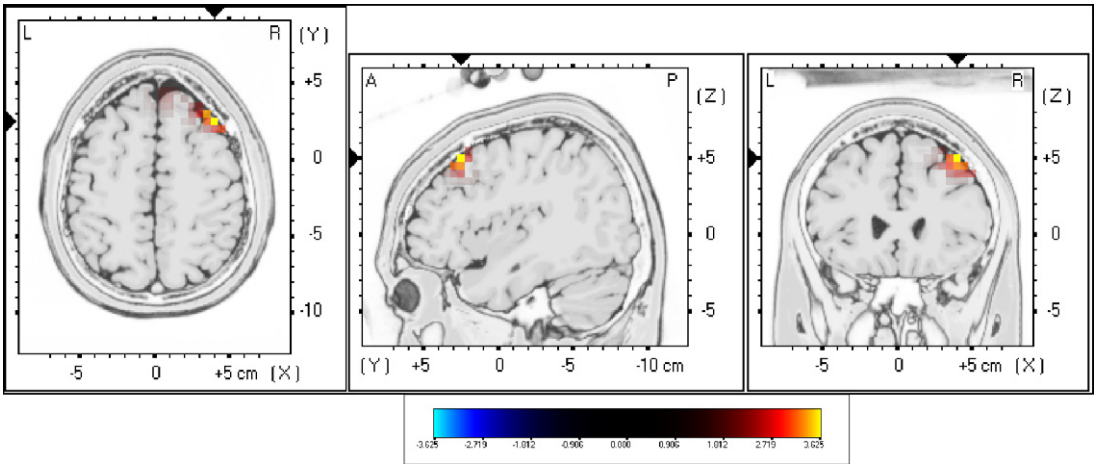

Fig. 2. sLORETA contrast analysis between unilateral versus NTE normative database ($p < .05$) revealed increased gamma (30.5–32 Hz) activity in the right superior premotor cortex (rMMC; BA8).

the superior premotor cortex, the parahippocampus, angular gyrus and the secondary auditory cortex area. These areas overlap with areas involved in tonal memory. Tonal memory activates a network comprising ventrolateral prefrontal cortex (encroaching Broca's area), dorsal premotor cortex, the planum temporal of the auditory cortex, inferior parietal lobe, the anterior insula, subcortical structures (basal ganglia and thalamus), as well as the cerebellum (Koelsch et al., 2009). The neurophysiological differences between a normative database and, respectively, unilateral tinnitus and bilateral tinnitus patients were also analyzed. That is, increased activity within the superior premotor cortex was noted for unilateral tinnitus versus control subjects and in the ventrolateral prefrontal cortex, frontopolar cortex and the superior premotor cortex for bilateral tinnitus versus control subjects. Comparison for left-sided and right-sided tinnitus separately with bilateral tinnitus revealed decreased synchronized beta2 activity in the superior premotor cortex and increased synchronized beta3 activity in parahippocampus and angular cortex for both left-sided and right-sided tinnitus in comparison to bilateral tinnitus. Furthermore, for left-sided tinnitus also increased synchronized

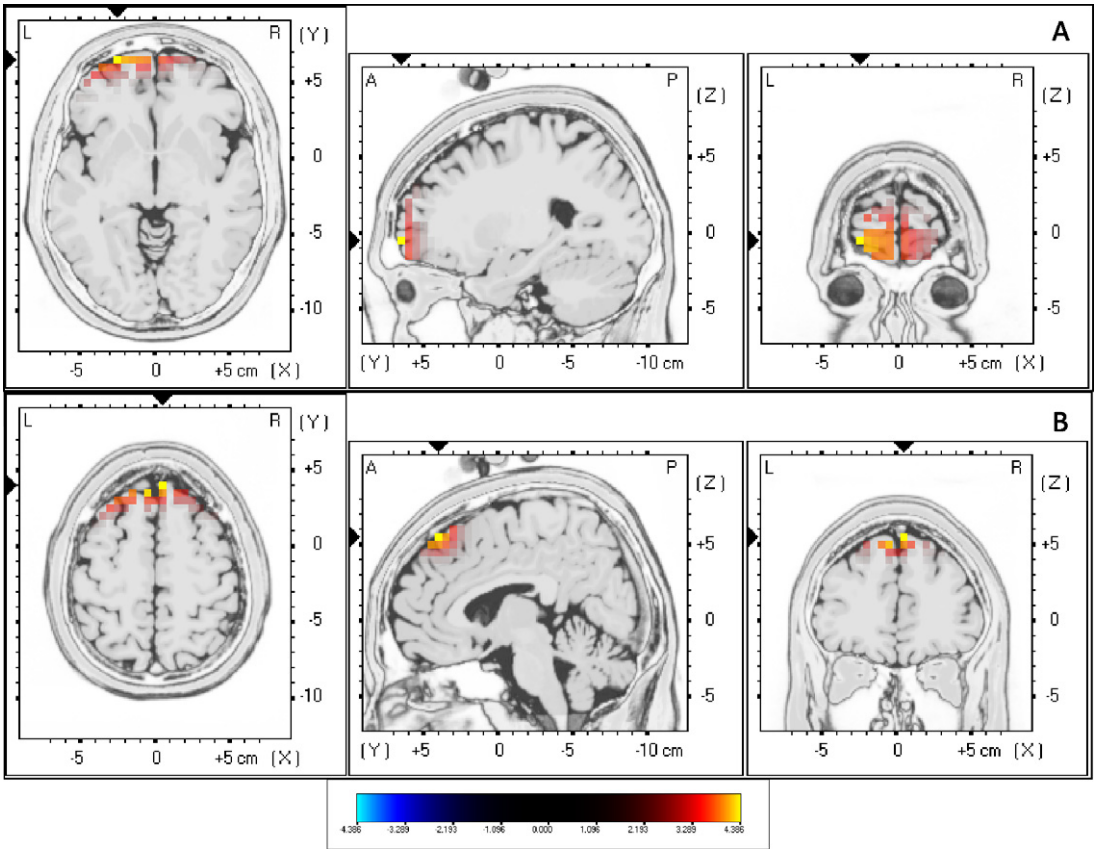

Fig. 3. sLORETA contrast analysis between bilateral tinnitus versus NTE normative database ($p < .05$): (A) increased beta1 (13–18 Hz) activity in ventrolateral prefrontal cortex and frontopolar cortex(LFG; BA47 and BA10) and (B) increased gamma (30.5–32 Hz) activity in the superiorprepremotor cortex (rMMC; BA8).

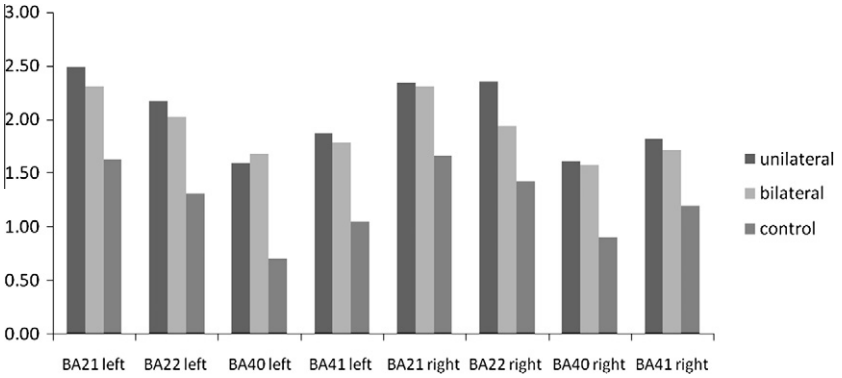

Fig. 4. Region of interest analysis for gamma band frequency (log-transformed current density).

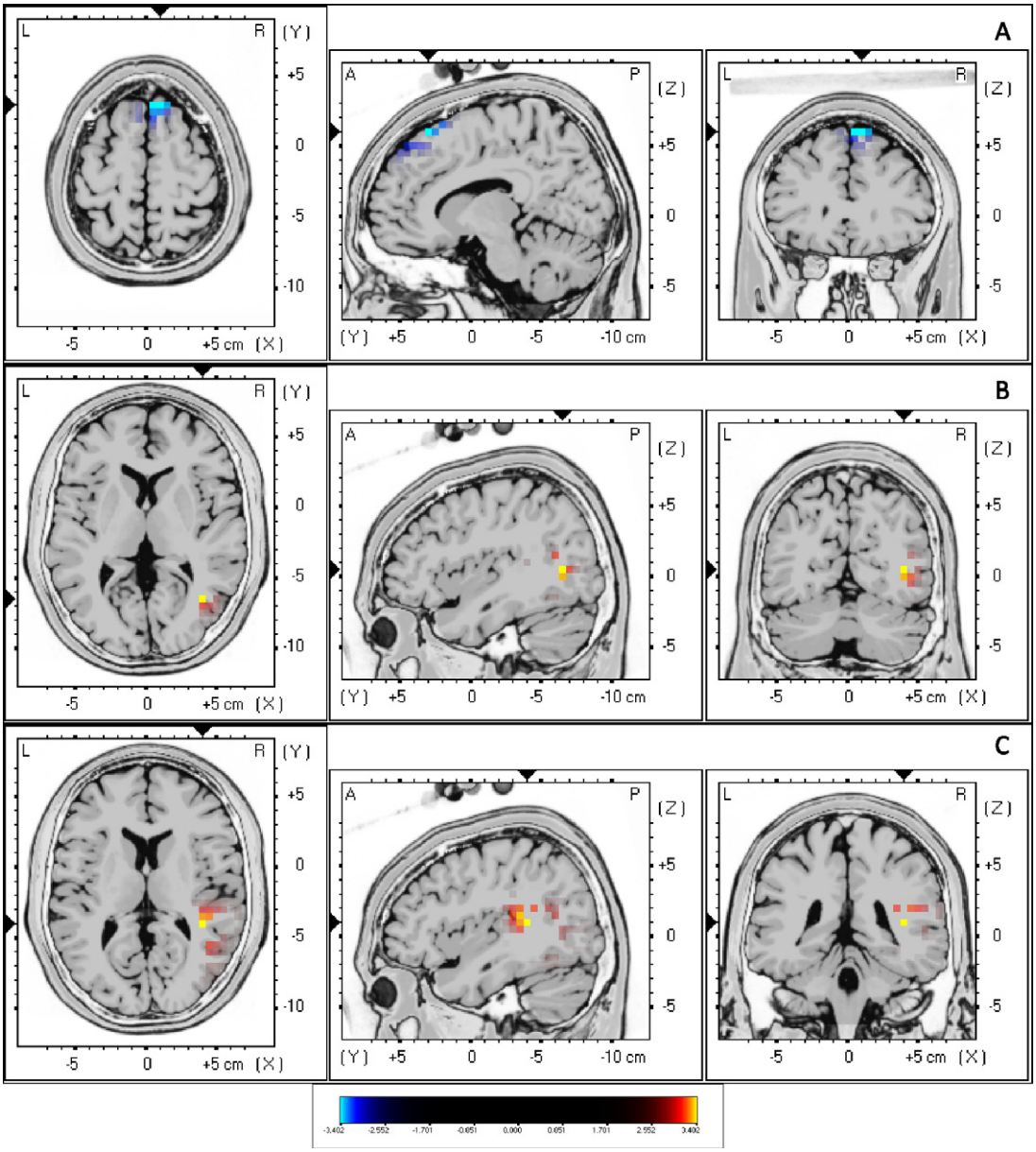

Fig. 5. sLORETA contrast analysis between left versus bilateral tinnitus ($p < .05$): (a) decreased beta2 (18.5–21 Hz) activity in the right superior premotor cortex (rMMC; BA6 and BA8), and (C and D) increased beta3 (21.5–30 Hz) and gamma (30.5–45 Hz) activity in, respectively, parahippocampal area (PHC; BA37) auditory cortex area (sAC; BA22) and the angular gyrus (BA39).

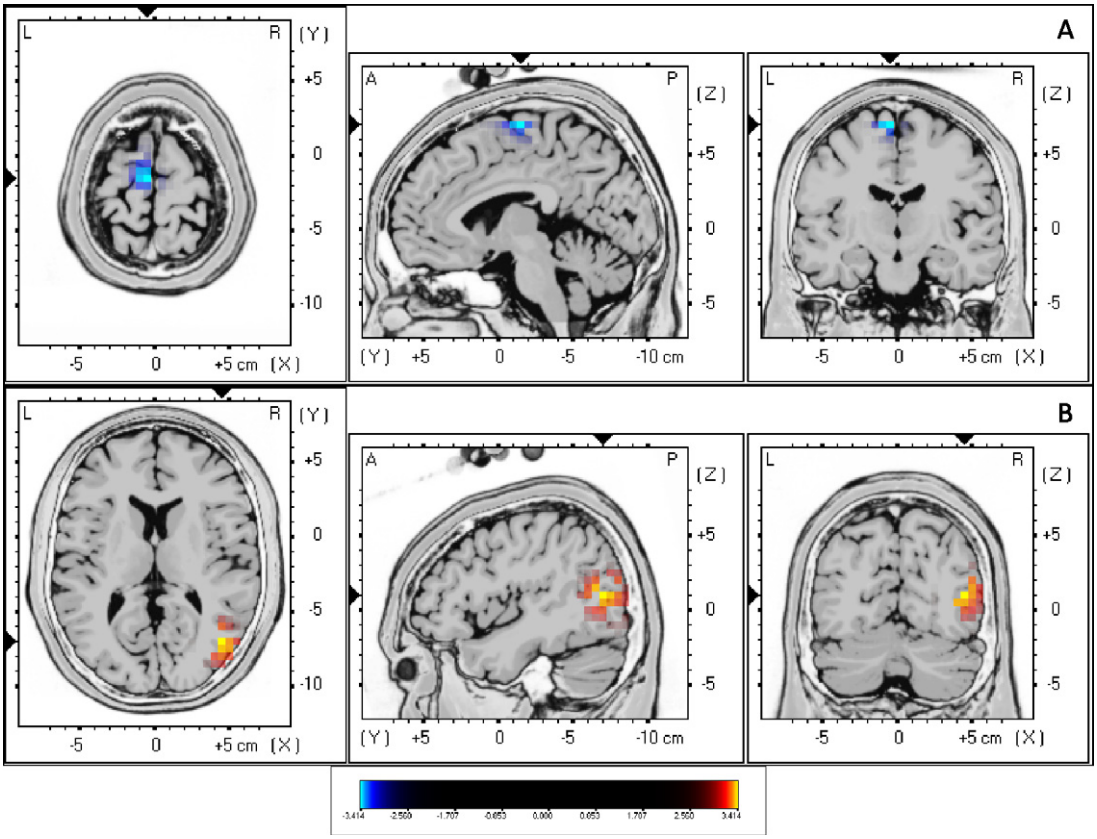

Fig. 6. sLORETA contrast analysis between Right versus Bilateral tinnitus ($p < .05$): (a) decreased beta2 (18.5–21 Hz) activity in the right superior premotor cortex (rMMC; BA6 and BA8), and (C)) increased beta3 (21.5–30 Hz) in, respectively, parahippocampal area (PHC; BA37) and the angular gyrus (BA39).

gamma activity in secondary/tertiary auditory cortex was found when comparing with bilateral tinnitus patients. A region of interest analysis for the gamma activity further revealed that in general tinnitus patients (both unilateral and bilateral) differ from the control subjects in gamma current density in the left and right primary and secondary auditory cortex. Table 2 gives an overview of the results.

Our results revealed differences in delta, beta and gamma activity when comparing unilateral tinnitus with bilateral tinnitus and beta and gamma activity when comparing, respectively, bilateral and unilateral tinnitus with control subjects.

In comparison to the normative database we found for both unilateral as well as bilateral tinnitus increased synchronized activity in the superior premotor cortex and ventrolateral prefrontal cortex. For an auditory stimulus to be consciously perceived, activation of the primary auditory cortex is a prerequisite but not sufficient (Boly et al., 2005; Laureys et al., 2000). 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. Primary auditory cortex activation might be only related to intensity coding (Jancke et al., 1998) and not the conscious percept per se, similarly to what has been demonstrated at a single cell level for somatosensory stimuli in the primary somatosensory cortex: stimulus intensity is encoded in the primary somatosensory cortex, while the conscious percept seems to be located in the frontal cortex (i.e. premotor cortex) (de Lafuente and Romo, 2005). Single cell recording in animals also revealed intensity related activity in the auditory cortex (Bandyopadhyay et al., 2010). Taking these findings together, we hypothesize synchronized activity in the superior premotor cortex might be involved in the conscious perception of the phantom sound, similarly to the conscious perception for somatosensory stimuli. This is in accordance with a PET study of tinnitus (Mirz et al., 2000) describing a right prefrontal–temporal network subserving tinnitus perception.

The premotor activation might also be related directly to a spatial localization function. A fMRI study, evaluating different auditory modalities (what, where, when), demonstrated that the superior part of the premotor cortex has a spatial localization

Table 2
Summary results.

BA	Putative function	Uni versus Control	Bil versus Control	Uni versus Bil	Left versus Bil	Right versus Bil
6/8	Where	rγ	l/rγ	$r\beta_2$	$r\beta_2$	$l\beta_2$
10	Attention		$l/r\beta_1$			
47	When		$l/r\beta_1$	lδ		
22	Auditory			$r\beta_3$, γ	rγ	
39	Spatial location multi-sensory integration			$r\beta_3$, γ	rγ	$r\beta_3$
37	Auditory sensory gating			$r\beta_3$, γ	$r\beta_3$, γ	$r\beta_3$

R, right; l, left; β_1, beta1; β_2, beta2; β_3, beta3; γ, gamma.

function (Schubotz et al., 2003) and the superior premotor activity was characterized by a co-activation of the angular gyrus (Schubotz et al., 2003).

Thus the premotor plus angular gyrus activity might actually reflect the spatial location of where the tinnitus is perceived and thus also the lateralization of the sound.

In addition, we found differences in the ventrolateral (pre)frontal cortex when comparing unilateral and bilateral tinnitus and bilateral tinnitus versus controls. This ventrolateral prefrontal cortex beta1 activity therefore seems to be specific for bilateral tinnitus. Interestingly, Schafer et al. recently showed that deactivation in the premotor cortex strongly correlated with activation in the inferior frontal gyrus (Schafer and Constable, 2009) and in this study increased delta activity of the ventrolateral prefrontal cortex is associated with a decrease in beta2 activity in the superior premotor cortex.

The ventrolateral prefrontal cortex involvement in bilateral tinnitus might reflect non-spatial auditory processing (Cohen et al., 2009), e.g. temporal auditory processing (Schubotz et al., 2003) rather than spatial processing, as this area is not involved in auditory spatial processing (Cohen et al., 2009). The increased delta activity might hypothetically result in modulation of the premotor area (Schafer and Constable, 2009), which then localizes (with the right inferior parietal area) the tinnitus to either the left or right side, based on the prevailing beta2 activity.

An important result is that compared to bilateral tinnitus, unilateral tinnitus evokes increased gamma-band activity in the right parahippocampal area as well the right secondary auditory cortex. Similar results were found for, respectively, left-sided tinnitus versus bilateral tinnitus and right-sided tinnitus versus bilateral tinnitus. Typically the parahippocampus has been associated both in animal and humans with auditory sensory gating, which is mediated by a network, including the auditory cortex, prefrontal cortex and the parahippocampus (Boutros et al., 2008, 2005; Grunwald et al., 2003; Korzyukov et al., 2007). Sensory gating involves suppression of redundant or irrelevant auditory information, and the parahippocampus is considered the entry to the auditory hippocampus (Tulving and Markowitsch, 1997). It has been hypothesized that the hippocampus could be constantly updating the tinnitus which is being generated in the thalamocortical system (De Ridder et al., 2006) preventing habituation. This parahippocampal gating mechanism possibly involves a direct hippocampal influence, preventing the tinnitus percept to be updated or to be pulled from hippocampal memory as previously proposed (De Ridder et al., 2006). Normally, when perceiving an external sound subjects elicit bilateral parahippocampal activation (Mayer et al., 2009; Wang et al., 2009). As such, bilateral activation might be considered the default mode of parahippocampal activity. However, if the parahippocampal area is only unilaterally activated this could hypothetically result in unilateral tinnitus. Preliminary support for this hypothesis can be found in this study revealing that only the right parahippocampal area shows increased synchronized activity for unilateral tinnitus. In addition, larger activity coherence in the contralateral parahippocampal area was also demonstrated within unilateral temporal lobe epilepsy patients during a left-sided and right-sided sensoripremotor task, while control subject showed increased activity bilaterally in the parahippocampal area (Wang et al., 2009). Langrebe et al. further revealed in a voxel-based morphometry study that the hippocampal area had reduced grey matter decreases in tinnitus patients (Landgrebe et al., 2009).

Increased synchronized activity was found in the auditory cortex and the angular gyrus for unilateral tinnitus patients and left-sided tinnitus patients. As there is a strong connection between the auditory cortex and the parahippocampus (Boutros et al., 2008, 2005; Grunwald et al., 2003; Korzyukov et al., 2007), it is possible that parahippocampal activity also results in auditory cortex activation and vice versa. Mayer et al. indeed found that when the right parahippocampal area becomes active also the right auditory cortex is active during listening to auditory stimuli (Mayer et al., 2009). The angular gyrus has already been associated with recollection-related activity (Daselaar et al., 2006) as well as for semantic processing and integration of auditory stimuli (Hickok et al., 2003; Raettig and Kotz, 2008). It is part of the temporoparietal area which has been implicated in tinnitus (Fregni et al., 2006; Khedr et al., 2008; Marcondes et al., 2010; Plewnia et al., 2003, 2007; Poreisz et al., 2009). The angular gyrus has strong reciprocal connections with parahippocampal area (Clower et al., 2001; Suzuki and Amaral, 1994) and is a key node in the dorsal auditory pathway, whose general main function is the transformation of auditory representations into premotor responses (Karabanov et al., 2009; Okada et al., 2003; Warren et al., 2005). The temporoparietal junction area, which includes the angular gyrus, is directly connected to the ventral and dorsal premotor cortices (Deacon, 1992; Petrides and Pandya, 2002) and the right inferior parietal area, including the angular gyrus, forms part of the 'where pathway' (Kaas and Hackett, 1999; Rauschecker and Scott, 2009) in auditory working memory. The right inferior parietal area is involved in monitoring and updating sound location independent of motor responding (Alain et al., 2008). Thus, co-activation of the angular area with the superior premotor cortex is important in spatial localization of auditory input (Schubotz et al., 2003).

Region of interest analysis demonstrated that both unilateral and bilateral tinnitus patients had more gamma activity in the left and right primary and secondary auditory cortices in comparison to the control group. Furthermore differences were found in the right secondary auditory cortex between unilateral and bilateral tinnitus. The reason why no differences in the left auditory cortex were noted might be related to the fact that functional changes within the auditory cortex are not strong enough to be detectable with whole brain analyses. Alternatively, specific tinnitus characteristics (e.g. pure tone tinnitus) may be accompanied by different activation patterns, not controlled for in this study, in the auditory cortex. Recent findings also suggest that the involvement of the auditory cortex in the pathophysiology of tinnitus might decrease with increasing tinnitus duration (De Ridder et al., 2005; Kleinjung et al., 2007; Schlee et al., 2009).

The comparison of, respectively, left-sided and right-sided tinnitus with bilateral tinnitus yielded differences in similar brain areas, namely the superior premotor cortex, the parahippocampus, and angular cortex area in the same frequency bands as when comparing the unilateral versus bilateral tinnitus. As such, the findings indicate to be quite reliable.

One limitation of the present study should be noted. There may be differences between the tinnitus group and the control group. As these two groups are not age-matched possible differences might be related to age. However, a recent EEG cortical sources study estimate by LORETA conducted by Babiloni et al. reveals that only for alpha1 and alpha2 significant differences are obtained for elderly in comparison to younger subjects (Babiloni et al., 2006). Secondly, as the control group was collected at a different laboratory it is possible that cultural background could also have an influence on the obtained results. However, cross-cultural assessment of neuropsychological performance and electrical brain function measures (i.e. EEG) revealed no significant differences across the three continents studied (Paul et al., 2007). Furthermore, individual alpha frequency peaks between difference groups revealed no significant differences in this analysis. Hence, it is likely that differences demonstrated between both tinnitus groups and the control groups in this study are reliable and valid, as well for intelligence. Further research with a perfectly matched group, if possible at all, is welcomed.

Why beta and gamma-band activity is differentially involved in different areas is unknown and cannot be explained yet. The (beta3 and) gamma-band activity in the auditory cortex, superior premotor cortex, parahippocampal area and angular gyrus suggest that these areas form one spatial localization network. The beta2 premotor activity seems to determine whether the tinnitus is perceived on the left or the right side. The left-sided delta activity in the ventrolateral prefrontal cortex most likely has no spatial function as it is only present in bilateral tinnitus.

In conclusion, differences in brain activity can be found in the parahippocampal area, angular gyrus, superior premotor cortex and ventrolateral prefrontal cortex between unilateral and bilateral tinnitus. These differences should be taken into account when evaluating functional neuroimaging data relating to tinnitus.

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