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# The neural network of phantom sound changes over time: a comparison between recent-onset and chronic tinnitus patients

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## Abstract

Tinnitus is characterized by an ongoing conscious perception of a sound in the absence of any external sound source. Chronic tinnitus is notoriously characterized by its resistance to treatment. In the present study the objective was to verify whether the neural generators and/or the neural tinnitus network, evaluated through EEG recordings, change over time as previously suggested by MEG. We therefore analyzed the source-localized EEG recordings of a very homogenous group of left-sided narrow-band noise tinnitus patients. Results indicate that the generators involved in tinnitus of recent onset seem to change over time with increased activity in several brain areas [auditory cortex, supplementary motor area and dorsal anterior cingulate cortex (dACC) plus insula], associated with a decrease in connectivity between the different auditory and nonauditory brain structures. An exception to this general connectivity decrease is an increase in gamma-band connectivity between the left primary and secondary auditory cortex and the left insula, and also between the auditory cortices and the right dorsal lateral prefrontal cortex. These networks are both connected to the left parahippocampal area. Thus acute and chronic tinnitus are related to differential activity and connectivity in a network comprising the auditory cortices, insula, dACC and premotor cortex.

## Introduction

Tinnitus is characterized by an ongoing conscious perception of a sound in the absence of any physical sound source. Hence it is considered an auditory phantom phenomenon similar to central neuropathic pain (Tonndorf, 1987; Moller, 2000). Tinnitus is perceived continuously by ~5–15% of the adult population. The neurobiological basis of tinnitus is characterized by an ongoing abnormal spontaneous activity and reorganization of the auditory central nervous system (Weisz *et al.*, 2005, 2007a,b; Moazami-Goudarzi *et al.*, 2010), but nonauditory brain structures such as the dorsal prefrontal cortex, anterior cingulate cortex, and the (para)hippocampus (Mirz *et al.*, 2000; De Ridder *et al.*, 2006; Muhlau *et al.*, 2006; Landgrebe *et al.*, 2009) are also involved in tinnitus, and how these areas co-activate has recently been investigated (Schlee *et al.*, 2009).

Several studies have shown that focal stimulation of the temporal cortex by repetitive transcranial magnetic stimulation (rTMS) (De Ridder *et al.*, 2005b; Kleinjung *et al.*, 2007; Plewnia *et al.*, 2007a) can suppress tinnitus perception. However, the amount of maximal tinnitus suppression by rTMS decreases with time (De Ridder *et al.*, 2005b; Plewnia *et al.*, 2007a; Kleinjung *et al.*, 2007; Khedr *et al.*, 2008).

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At least two different hypotheses can be proposed to explain why tinnitus is more difficult to suppress if the tinnitus duration increases. Firstly, it is possible that the neural generators change over time, i.e. new areas become involved in tinnitus generation and the auditory cortex becomes less involved over time. Another possibility can be proposed in which the neural connectivity within the same network changes over time. In a recent magnetoencephalographic (MEG) connectivity study with selected ROIs it was shown that in patients with recent tinnitus onset (i.e. < 4 years) the gamma network connections are concentrated in the left temporal area (auditory cortex) while in chronic tinnitus patients (i.e. > 4 years) the network is widely distributed over the entire cortex, with less involvement of the auditory temporal areas (Schlee *et al.*, 2009). However, the two propositions are not mutually exclusive. It is possible that both the neural generator and neural connectivity change with increasing tinnitus duration.

In the present research the objectives were to verify whether new neural generators arise and/or whether the neural tinnitus network changes over time. We used the source-localized electroencephalographic (EEG) recordings of a homogenous group of unilateral left-sided narrow-band noise tinnitus patients and analyzed the spectral components related to the tinnitus duration as well as the connectivity within a group of selected regions of interest (ROIs). The ROIs were chosen based on areas involved in tinnitus according to the positron emission tomography (PET), single-photon emission computed

tomography (SPECT), magnetoencephalography (MEG), EEG and voxel-based morphometry (VBM) tinnitus literature.

## Materials and methods

### *Patients*

Eighteen patients ($N = 18$; nine males and nine females) with strictly unilateral left-sided narrow-band noise tinnitus with a mean age of 60.82 years were selected from the multidisciplinary Tinnitus Research Initiative (TRI) Clinic of the University Hospital of Antwerp, Belgium. None of the patients included in this study had been treated with rTMS prior to the study. Individuals with pulsatile tinnitus, Ménière's disease, otosclerosis, chronic headache and neurological disorders such as brain tumors, and individuals being treated for mental disorders, were excluded from the study in order to obtain a very homogeneous sample. As such, 10 patients with tinnitus of recent onset (< 4 years) and eight patients with chronic tinnitus (> 4 but < 10 years) were selected. The 4-year cutoff was based on the available tinnitus literature. Results of microvascular decompression (Moller *et al.*, 1993; Brookes, 1996; Jannetta, 1997; Ryu *et al.*, 1998; De Ridder *et al.*, 2004, 2005a, 2007, 2010) and transcranial magnetic stimulation (De Ridder *et al.*, 2005b; Plewnia *et al.*, 2007a; Kleinjung *et al.*, 2007; Khedr *et al.*, 2008) suggest that tinnitus results worsen over time, with a turning point of efficacy between 3 and 5 years. This fits with a magnetoencephalographic study that demonstrates that after 4 years the tinnitus-generating network changes its connectivity (Schlee *et al.*, 2009).

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 beverage consumption on the day of recording. Each 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 (TQ; Meeus *et al.*, 2007) was used to asses tinnitus related distress. A Mann–Whitney *U*-test was conducted to verify differences between both groups for age, tinnitus duration, VAS, TQ, and Hearing loss. No significant differences were found between recent-onset and chronic tinnitus patients for age, VAS or 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.

Also, an age- and gender-matched control group ($N = 12$; mean ± SD, 61. 32 ± 10.91 years; six males and six females) was collected. None of these subjects was known to suffer from tinnitus. Exclusion criteria were known psychiatric or neurological illness, psychiatric history, abuse of drugs or alcohol, history of head injury (with loss of consciousness), seizures, headache, or physical disability in a participant. To our knowledge the tinnitus patients did not differ from the control group in any aspect except their tinnitus.

### *EEG data collection*

EEG recordings (Mitsar-201; NovaTech http://www.novatecheeg.com/) were obtained in a quiet and dimly lighted room with each participant sitting upright on a small but comfortable chair. This EEG system is used by several research groups over the world (Sherlin *et al.*, 2007; Mueller *et al.*, 2010; Phlypo & Congedo, 2010). The actual recording lasted ∼5 min. 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 ears, and impedances were checked as remaining below 5 kΩ. Data were collected with eyes closed (sampling rate 1024 Hz, bandpass-filtered 0.15–200 Hz). Data were resampled to 128 Hz, bandpass-filtered (fast Fourier transform filter) to 2–44 Hz and subsequently transposed into Eureka! Software (Congedo, 2002), plotted and carefully inspected with manual rejection of artifacts. All episodic artifacts including eye blinks, eye movements, teeth clenching, body movement and ECG artifacts were removed from the stream of the EEG. Average Fourier 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 (30.5–44 Hz).

Table 1. Patients' characteristics

| | Duration | | |
|---|---|---|---|
| | Recent onset | Chronic | *P*-value |
| Sex | | | |
| Male | 5 | 4 | – |
| Female | 5 | 4 | |
| Age | | | |
| M | 59.78 | 62.12 | 0.74 |
| SD | 10.62 | 12.43 | |
| Tinnitus duration | | | |
| M | 1.72 | 8.00 | 0.001 |
| SD | 0.62 | 1.85 | |
| VAS intensity | | | |
| M | 6.43 | 7.43 | 0.21 |
| SD | 1.40 | 1.27 | |
| TQ | | | |
| M | 53.00 | 53.80 | 0.79 |
| SD | 10.73 | 9.86 | |
| Tinnitus frequency (Hz) | | | |
| M | 4937.50 | 4720.83 | 0.85 |
| SD | 2771.14 | 2777.08 | |
| Hearing loss* (dB HL) | | | |
| M | 26.83 | 35.00 | 0.28 |
| SD | 20.55 | 15.37 | |

*Mean HL at the tinnitus frequency

### *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 × 5 × 5 mm) and is restricted to cortical gray matter and hippocampi, as defined by digitized Montreal Neurological Institute (MNI)152 template (Fuchs *et al.*, 2002). Scalp electrode coordinates on the 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 functional magnetic resonance imaging (fMRI; Vitacco *et al.*, 2002; Mulert *et al.*, 2004), structural MRI (Worrell *et al.*, 2000) and PET (Dierks *et al.*, 2000; Pizzagalli *et al.*, 2004; Zumsteg *et al.*, 2005), and has been used in previous studies to detect for example activity in the auditory cortex (Zaehle *et al.*, 2007; Vanneste *et al.*, 2011). Further sLORETA validation has been based on accepting as

ground truth the localization findings obtained from invasive, implanted depth electrodes, of which there are several studies in epilepsy (Zumsteg *et al.*, 2006a,c) and cognitive event-related potentials (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 & Praamstra, 2001). The intracerebral volume is partitioned into 6239 voxels at 5-mm spatial resolution. Thus, sLORETA images represent the standardized electrical 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).

### *Functional connectivity*

Brain connectivity can refer to a pattern of anatomical links (anatomical connectivity), of statistical dependencies (functional connectivity) or of causal interactions (effective connectivity) between distinct units within a nervous system. The present research focuses on functional connectivity which captures deviations from statistical independence between distributed and often spatially remote neuronal units. Statistical dependence may be estimated by measuring correlation or covariance, spectral coherence or phase-locking. Functional connectivity is often calculated between all elements of a system, regardless of whether these elements are connected by direct structural links. Unlike structural connectivity, functional connectivity is highly time-dependent. Statistical patterns between neuronal elements fluctuate on multiple time scales, some as short as tens or hundreds of milliseconds. It should be noted that functional connectivity does not make any explicit reference to specific directional effects or to an underlying structural model.

Coherence and phase synchronization between time-series corresponding to different spatial locations are usually interpreted as indicators of the connectivity. However, any measure of dependence is highly contaminated with an instantaneous, nonphysiological contribution due to volume conduction (Pascual-Marqui, 2007b). However, Pascual-Marqui (2007a) introduced a new technique (i.e. Hermitian covariance matrices) that removes this confounding factor. 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, and are defined in the frequency domain: 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). Based on this principle lagged linear connectivity was calculated. ROIs were defined based on previous brain research on tinnitus (see Table 2 for overview).

### *ROI analysis*

The log-transformed electrical current density was averaged across all voxels belonging to the ROI. ROIs were the left and right primary auditory cortices [Brodmann area (BA)40 and BA41 respectively] and the left and right secondary auditory cortex (BA21 and BA22), and were predefined based on the MNI coordinates, belonging to a specific Brodmann area on a standard brain. ROI analysis were computed for the different frequency bands separately.

A multivariate ANOVA (i.e. Wilks' Lambda) was used for the different frequency bands with the respective ROIs [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 (recent-onset, chronic and control subjects) as independent variables. A Bonferroni correction was applied for multiple comparisons.

TABLE 2. Regions of interest

| | Authors |
|---|---|
| Amygdala | De Ridder *et al.* (2006) and Landgrebe *et al.* (2009) |
| Anterior cingulate cortex | |
| Dorsal | Plewnia *et al.* (2007b), Vanneste *et al.* (2010) and Schlee *et al.* (2009) |
| Subgenual | Muhlau *et al.* (2006) and Vanneste *et al.* (2010) |
| Auditory cortex | Muhlnickel *et al.* (1998), Schneider *et al.* (2009), Smits *et al.* (2007) and Weisz *et al.* (2007a,b) |
| Dorsal lateral prefrontal cortex | Mirz *et al.* (2000) |
| Insula | Smits *et al.* (2007) and Vanneste *et al.* (2010) |
| Parahippocampus | Landgrebe *et al.* (2009) |

### *Statistical analyses*

The methodology used is nonparametric. It is based on estimating, via randomization, the empirical probability distribution for the max-statistic, under the null hypothesis comparisons (Nichols & Holmes, 2002). This methodology corrects for multiple testing (i.e. for the collection of tests performed for all voxels, and for all frequency bands). Due to the nonparametric nature of the method, its validity does not rely on any assumption of Gaussianity (Nichols & Holmes, 2002).

sLORETA statistical contrast maps were calculated through multiple voxel-by-voxel comparisons in a logarithm of the *F*-ratio. The significance threshold was based on a permutation test with 5000 permutations. A comparison was made between the tinnitus group (recent-onset and chronic tinnitus group) and control subjects as well as between the chronic tinnitus group and the group with tinnitus of recent onset.

Connectivity contrast maps were calculated through multiple voxel-by-voxel comparisons using *t*-statistics. The significance threshold was based on a permutation test with 5000 permutations. Again, a comparison was made between the tinnitus group (recent-onset and chronic tinnitus group) and control subjects as well as between chronic tinnitus and tinnitus with recent onset.

To further confirm our connectivity analysis we conducted a split-half reliability analysis. We randomly divided individuals for each of the recent-onset and chronic groups into two groups and conducted similar connectivity analyses between the recent-onset and chronic group for both groups.

## Results

### *Neural generators – tinnitus vs. control*

A comparison between tinnitus patients and control subjects revealed significant differences for theta, beta2, beta3 and gamma frequency bands. Increased activity could be found for tinnitus patients in,

respectively, the supplementary motor area (BA6) for theta, the dorsal anterior cingulate (BA24) for beta2 and beta3 and the right parahippocampal area (BA37) for gamma (see Fig. 1; $P < 0.05$). No significant differences could be retrieved for the delta, alpha1, alpha2 or beta1 frequencies.

### *Neural generators – chronic tinnitus vs. tinnitus of recent onset*

The same frequencies as when comparing tinnitus patients with the control group showed significant differences between chronic tinnitus and tinnitus with recent onset. Increased spontaneous electrical activity could be found for chronic tinnitus patients in comparison to tinnitus patients with recent onset, in the supplementary motor area (BA6) for theta, the dorsal anterior cingulate (BA24 and BA32) for beta2 and beta3, the insula (BA13) for beta3 and the auditory cortex (BA21 and BA22) for gamma (see Fig. 2; $P < 0.05$). No significant differences could be retrieved in delta, alpha1, alpha2 or beta1 frequencies.

### *ROI analysis*

A significant effect was found for the log-transformed current density for the different groups on the ROI for the gamma frequency band ($F_{8,48} = 2.43$, $P < 0.05$; see Table 3). Including all frequency bands next to the gamma frequency band in one analysis did not result in a significant effect. However, this significant effect might remain if the sample size increased.

Univariate ANOVA further yielded significant effects for left primary auditory cortex ($F_{2,27} = 3.54$, $P < 0.05$), right primary auditory cortex ($F_{2,27} = 5.32$, $P < 0.05$), left secondary auditory cortex ($F_{2,27} = 4.84$, $P < 0.05$) and right secondary auditory cortex ($F_{2,27} = 9.30$, $P < 0.001$). A Bonferroni multiple comparison analysis ($P < 0.05$) revealed that the control subjects had significant lower log-averaged current density than either recent-onset tinnitus or chronic tinnitus patients for the left and right primary auditory cortex. Chronic tinnitus was significantly different from tinnitus with recent onset for the left and right secondary auditory cortex. No significant effect was obtained for the other frequency bands ($P > 0.25$).

### *Neural connectivity – tinnitus vs. control*

A comparison between tinnitus patients and control subjects demonstrated significant differences for theta, alpha2 and gamma frequency bands (see Figs 3 and 4; $P < 0.05$). Decreased functional connectivity could be found in general for these three frequency bands for tinnitus patients in comparison to control subjects. Increased synchronized activity could be found for tinnitus patients in comparison to control subjects within the theta (4–7.5 Hz) band between the left and right parahippocampal area (BA37) and in alpha2 (10–12 Hz) connectivity between the left parahippocampal area (BA37) and the left auditory cortex (BA21, BA22), and the right parahippocampal area (BA37) and the right auditory cortex (BA21, BA22; see Fig. 3; $P < 0.05$). In addition, gamma (30–45 Hz) connectivity was increased between the left parahippocampal area (BA37) and the left and right auditory cortex (BA21, BA22) for tinnitus patients in comparison to control subjects (see Fig. 4; $P < 0.05$). No significant differences could be retrieved in delta, alpha1, beta1, beta2 or beta3 frequencies.

### *Neural connectivity – chronic tinnitus vs. tinnitus of recent onset*

Connectivity analysis yielded a significant difference between chronic tinnitus and tinnitus with recent onset for theta, alpha2 and gamma frequencies (see Figs 5 and 6; $P < 0.05$). Decreased phase-lagged connectivity could be found in general for these three frequency bands for chronic tinnitus patients in comparison to tinnitus of recent onset. Furthermore, a significant increase in phase-lagged connectivity could be found for the gamma band between the left parahippocampal area (BA37), left primary and non-primary auditory cortices (BA21, BA22, BA41 and BA42), the left insula (BA13) and the right dorsal lateral prefrontal cortex (DLPFC; BA9 and BA46) for chronic tinnitus patients. Two closed connectivity loops were discerned. The first was between the insula and BAs 21, 22, 41 and 42 of the auditory cortex. A second closed connectivity loop was found between DLPFC, and BA21, BA22 and BA41, BA42 of the auditory cortex (See Fig. 3, below panel).

The split-half reliability estimate showed similar results for both theta (see Supporting Information Fig. S1) and gamma bands (see Supporting Information Fig. S3) between the chronic group and the acute tinnitus group. That is, decreased phase-lagged connectivity could be found in general for these frequency bands for chronic tinnitus patients in comparison with tinnitus patients with recent onset. For alpha2 similar results were also obtained although with a decrease in phase-lagged connectivity for chronic tinnitus patients in comparison to tinnitus patients with recent onset (see Supporting Information Fig. S2). Some differences with the frontal areas were noted between the two split-half groups but these disappeared when the two groups were combined. In addition, significant increases in functional connectivity could be found for the gamma band between: (i) the left-sided parahippocampal area and primary and non-primary auditory cortices, and (ii) the insula to the tinnitus side and the right-sided DLPFC for chronic tinnitus patients in both groups, with two closed connectivity loops. These latter findings further confirm the reliability of our results.

TABLE 3. Region of interest comparison between patient with recent onset tinnitus, chronic tinnitus and control subjects for the primary and secondary auditory cortex in gamma band frequency

| | Recent onset | Chronic | Control |
|---|---|---|---|
| primary AC | | | |
| left | 1.77[a] | 2.22[a] | 1.33[b] |
| right | 1.72[a] | 2.49[a] | 1.42[b] |
| secondary AC | | | |
| left | 3.04[a] | 3.24[b] | 1.84[c] |
| right | 2.54[a] | 3.55[b] | 1.88[a] |

[a, b, c]Significant differences between recent onset tinnitus, chronic tinnitus and control subjects (Bonferroni correction for multiple comparisons).

## Discussion

The main objective of this study was to characterize the differences in neural generators and the neural network between tinnitus of recent onset and chronic tinnitus in a very homogenous group. When comparing the tinnitus group with a control group, we found differences within the anterior cingulate, medial premotor cortex and parahippocampal area. Differences were demonstrated in auditory areas (primary auditory cortex) as well as in nonauditory areas (anterior cingulate, insula and medial premotor cortex) for the chronic tinnitus group in comparison to the tinnitus of recent onset group. ROI analysis further revealed that the control subjects had significantly lower log-averaged current density in comparison to both recent-onset tinnitus and chronic tinnitus patients for the left and right primary

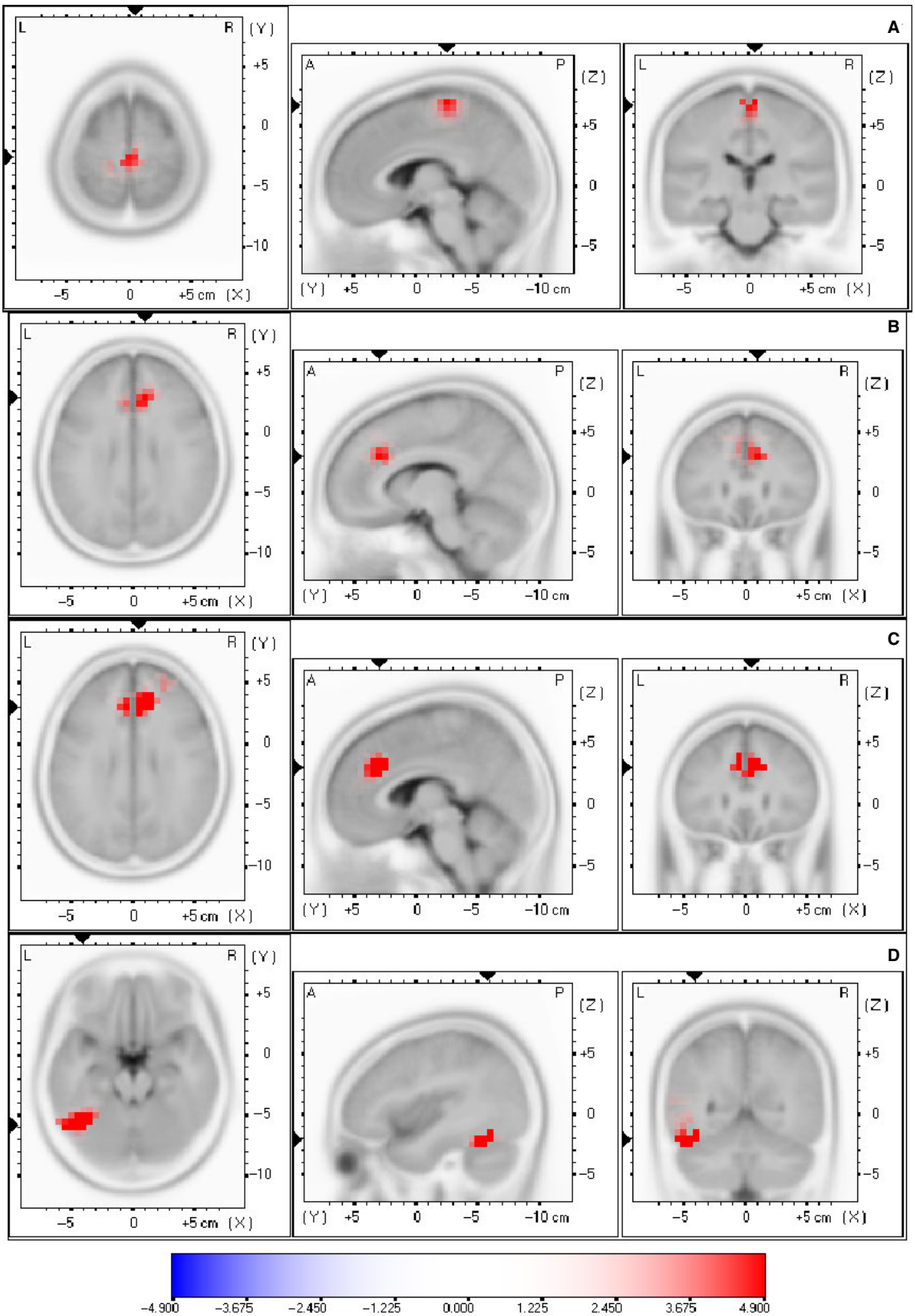


FIG. 1. sLORETA contrast analysis between tinnitus patients and control group ($P < 0.05$). Increased neural synchronization within (A) theta (4–7.5 Hz), (B) beta2 (18.5–21 Hz), (C) beta3 (21.5–30 Hz), and (D) gamma (30.5–45 Hz) in, respectively, (A) supplementary motor area (BA6), (B) right dorsal anterior cingulate (BA24 and BA32), (C) right dorsal anterior cingulate (BA24), and (D) parahippocampal area (BA19 and BA37) for tinnitus patients. L, left; R, right; A, anterior; P, posterior.

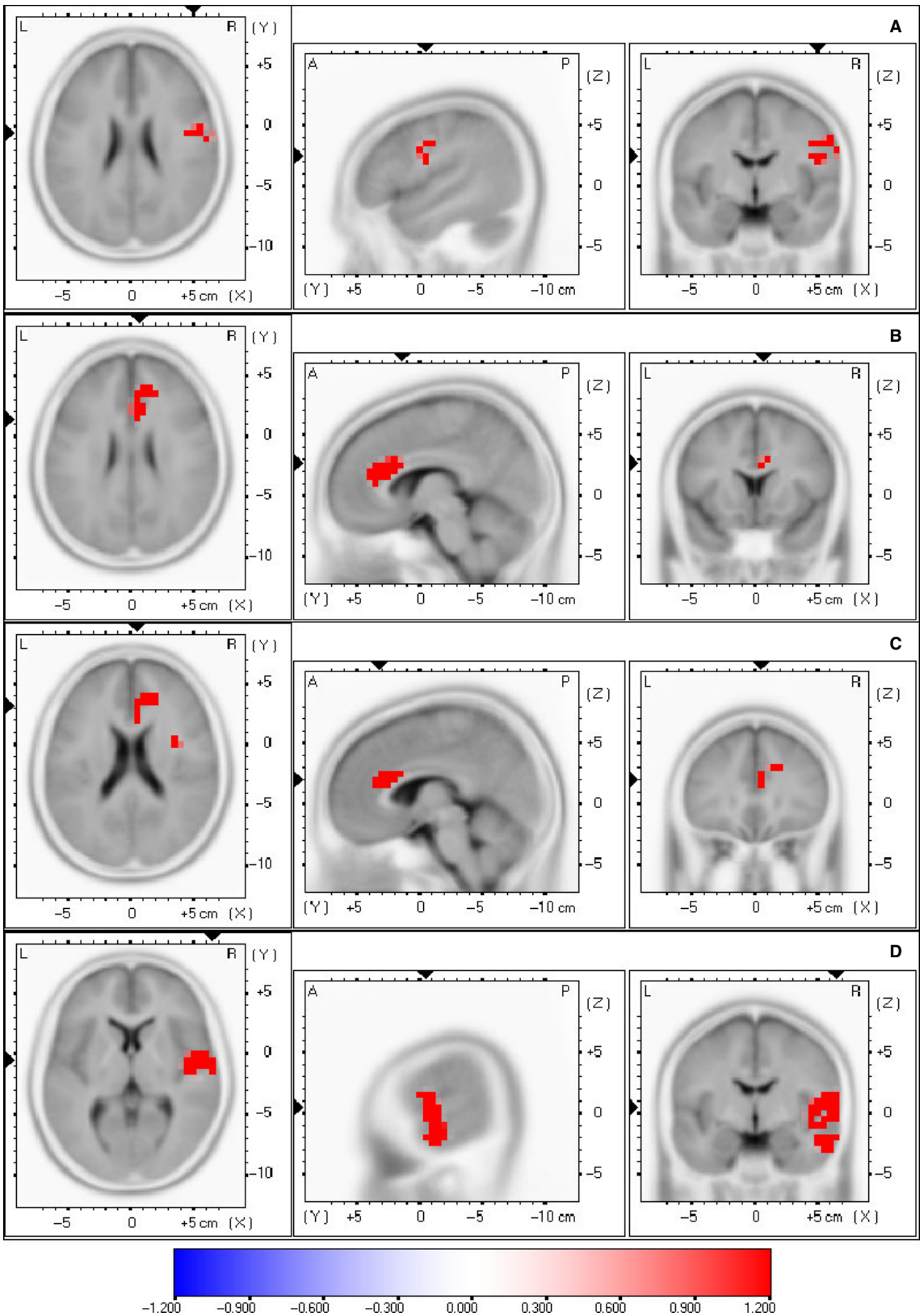


FIG. 2. sLORETA contrast analysis between chronic tinnitus patients and tinnitus patients with recent onset ($P < 0.05$). Increased neural synchronization within (A) theta (4–7.5 Hz), (B) beta2 (18.5–21 Hz), (C) beta3 (21.5–30 Hz), and (D) gamma (30.5–45 Hz) in, respectively, (A) right lateral premotor area (BA6), (B) right dorsal anterior cingulate (BA24 and BA32), (C) right dorsal anterior cingulate (BA24 and BA32) and right insula (BA13), and (D) right auditory cortex (BA21 and BA22) for chronic tinnitus patients. L, left; R, right; A, anterior; P, posterior.

auditory cortex. Furthermore, chronic tinnitus patients had significantly higher log-averaged current density in comparison to tinnitus with recent onset for the left and right secondary auditory cortex.

Differences were also found in the neural network with a decreased functional connectivity between the different ROIs for theta, alpha and gamma frequency band for tinnitus patients in comparison to the control subjects as well as in the chronic tinnitus patients in comparison to the tinnitus patients of recent onset. Increased phase-lagged connectivity could be seen for tinnitus patients in comparison to control subjects in the theta frequency band between the left and right parahippocampal area and in alpha2 between the left parahippocampal area and the left auditory cortex, and the right parahippocampal area and the right auditory cortex. Increased phase-lagged connectivity was found in the gamma band between the left parahippocampal area and the left and right auditory cortex for tinnitus patients in comparison to control subjects. Increased gamma-band connectivity was also found between the left parahippocampal area and primary auditory cortex, the left auditory cortex and right auditory cortex, and the left auditory cortex and left insula, as well as between the left auditory cortices and the right DLPFC for chronic tinnitus in comparison to tinnitus of recent onset.

### *Auditory cortex, parahippocampal area and supplementary motor area*

Increased gamma activity was found for tinnitus patients in comparison to control subjects in the parahippocampal area. This might be related to the constant updating of the tinnitus percept, preventing habituation (De Ridder *et al.*, 2006). Cells in the human hippocampus and parahippocampal areas respond to novel stimuli with an increase in firing. However, even 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 (Viskontas *et al.*, 2006), suggesting a rapid habituation. This rate of response decrement during trains of several stimulus repetitions is linear for acoustic responses (Wilson *et al.*, 1984). 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 (Viskontas *et al.*, 2006). Thus a novel stimulus is normally associated with parahippocampal habituation and active hippocampal inhibitory activity. Repetitive auditory stimuli both in animals (Bickford *et al.*, 1993) and humans (Boutros *et al.*, 2008) lead to attenuation of event-related potentials, but with differences in hippocampal and parahippocampal areas, as early hippocampal event-related potentials are not attenuated, in accordance with the abovementioned single-cell recordings. Based on these data it can be hypothesized that in tinnitus this mechanism is disrupted with persistent parahippocampal activity, preventing habituation. It has been hypothesized that the parahippocampal area plays 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). In line with this hypothetical mechanism, tinnitus can be seen as a result of constant sending of stored auditory information from the hippocampus to the auditory association areas by persistent parahippocampal activity.

For chronic tinnitus patients increased gamma activity was also found in the right auditory cortex in comparison to patients with recent-onset tinnitus, and an ROI analysis demonstrated increased gamma current density in tinnitus patients both in left- and right-sided primary and secondary auditory cortices. MEG data support thalamocortical dysrhythmia as the pathophysiological model for the development of gamma-band activity related to the tinnitus percept (Llinás *et al.*, 1999). According to this model tinnitus is caused by an abnormal, spontaneous and constant gamma-band activity (> 30 Hz) generated as a consequence of deafferentation-induced hyperpolarization of the medial geniculate body. In normal circumstances auditory stimuli increase thalamocortical rhythms to gamma-band activity (Joliot *et al.*, 1994). In the deafferented state, however, oscillatory alpha activity decreases to theta-band activity (4–7 Hz; Steriade, 2006). As a result lateral inhibition is reduced, inducing a surrounding gamma-band activity known as the 'edge effect' (Llinás *et al.*, 2005). This abnormally persistent coupled theta–gamma band dysrhythmia is relayed to the cortex, selectively in the deafferented thalamocortical columns. It has been proposed that synchronized gamma-band activity in the auditory cortex binds auditory events into one coherent conscious auditory percept (Ribary *et al.*, 1991; Llinas *et al.*, 1998; Crone *et al.*, 2001). The decrease in alpha activity and associated gamma-band activity has been shown to exist in tinnitus (Lorenz *et al.*, 2009). However, why there was more activity in the right auditory cortex for chronic left-sided tinnitus patients it not yet established, but a hypothesis can be proposed. Our results reveal that there was increased gamma connectivity between the left and right auditory cortex via the left parahippocampal area for tinnitus patients in comparison to control subjects. ROI analysis further demonstrated that both the left and right auditory cortex have a higher gamma current density in chronic tinnitus in comparison to the control group and that the left auditory cortex for chronic tinnitus patients is involved in closed loop with the insula as well as with the DLPFC. The reason why only the right auditory cortex is hyperactive in the gamma band and not the left auditory cortex in the global brain analysis might be related to the fact that tinnitus intensity is correlated to increased contralateral gamma-band activity (van der Loo *et al.*, 2009), increasing the right gamma-band activity even more in the right auditory cortex.

For tinnitus patients increased theta activity was also found in the supplementary motor area in comparison to a control group, as well as in the right supplementary motor area for patients with chronic tinnitus in comparison to patients with recent-onset tinnitus. The (visual) global workspace model has been suggested as a model for the awareness component of consciousness (Dehaene *et al.*, 2006). It proposes that conscious perception of sensory events requires sensory cortex activation embedded in a larger cortical network, the global workspace, extending beyond the primary sensory regions including prefrontal, parietal and cingulate cortices (Dehaene *et al.*, 2006). Therefore, to be aware of an auditory stimulus, activation of the primary auditory cortex is a prerequisite but is not sufficient (Laureys *et al.*, 2000; Boly *et al.*, 2005). 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 (Boly *et al.*, 2004). Primary auditory cortex activation might be only related to intensity coding (Jancke *et al.*, 1998) and not the percept *per se*. Melloni and colleagues found that theta oscillations in the frontal regions are essential for conscious perception during the maintenance interval of visual stimuli (Melloni *et al.*, 2007). Taking these findings together, we propose that synchronized gamma activity in the auditory cortex is responsible for the tinnitus intensity (van der Loo *et al.*, 2009), while synchronized theta activity in the supplementary motor area might be accountable for the conscious perception of the phantom sound, analogous to the conscious perception for somatosensory stimuli (de Lafuente & Romo, 2002, 2005, 2006). The functional heterogeneity of the supplemental motor area (SMA) has been shown

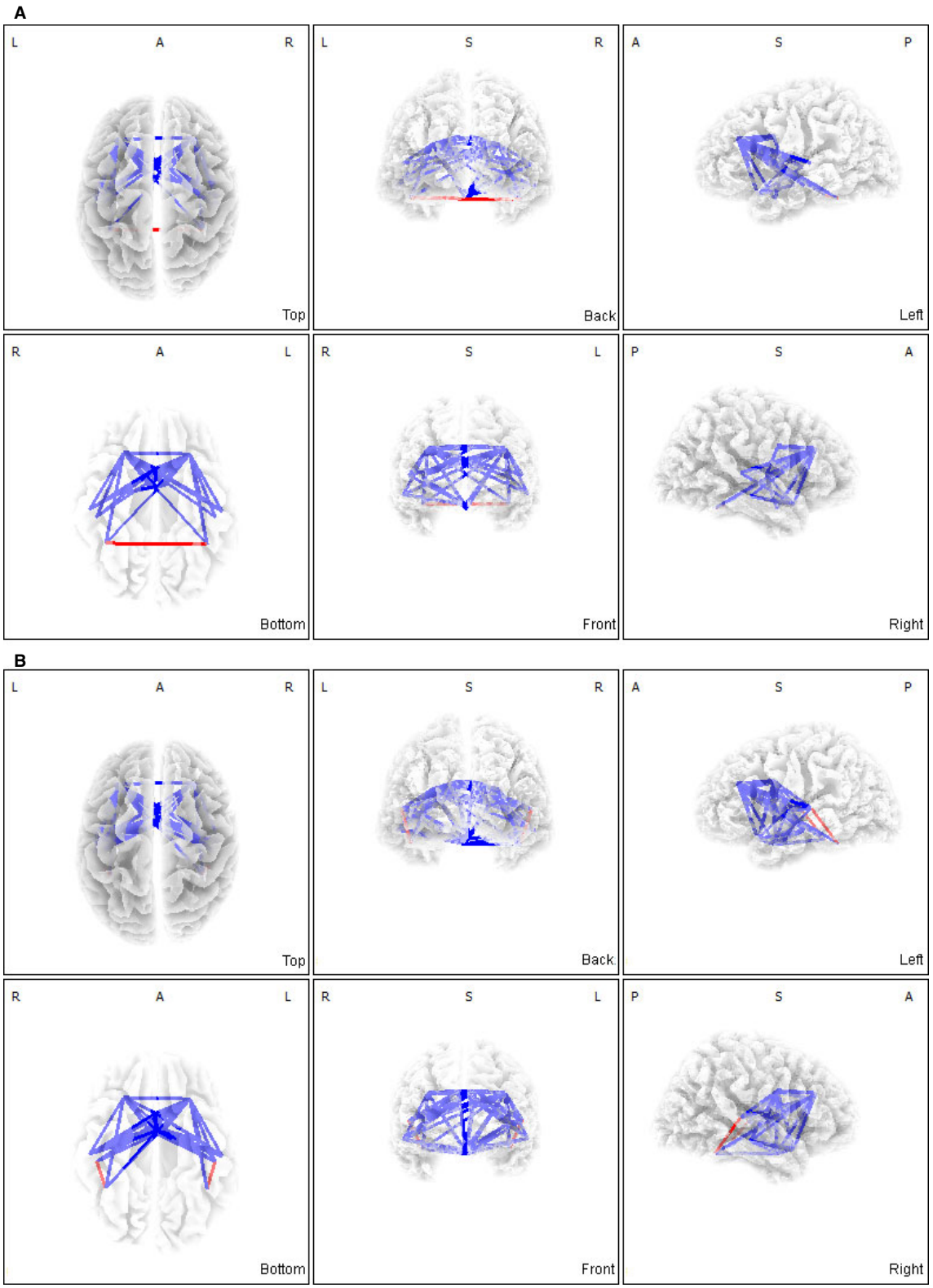


FIG. 3. Connectivity contrast analysis between tinnitus patients and control group ($P < 0.05$). Decreased neural phase-lagged synchronization within (A) theta (4–7.5 Hz) and (B) alpha2 (10–12 Hz) connectivity in tinnitus patients. An increased neural phase-lagged theta (4–7.5 Hz) synchronization can be seen between the left and right parahippocampal area and an increased neural phase-lagged alpha2 (10–12 Hz) synchronization is evident between the left parahippocampal area and the left auditory cortex and the right parahippocampal area and the right auditory cortex. L, left; R, right; A, anterior; P, posterior; S, superior.

before and demonstrates that the SMA has multiple functions, including motor, sensory, word generation and working memory functions (Chung *et al.*, 2005). The SMA is also activated in both auditory imagery and auditory hallucinations (Linden *et al.*, 2011), two conditions of auditory perception without and external sound source, analogous to tinnitus. This might be related to illusionary

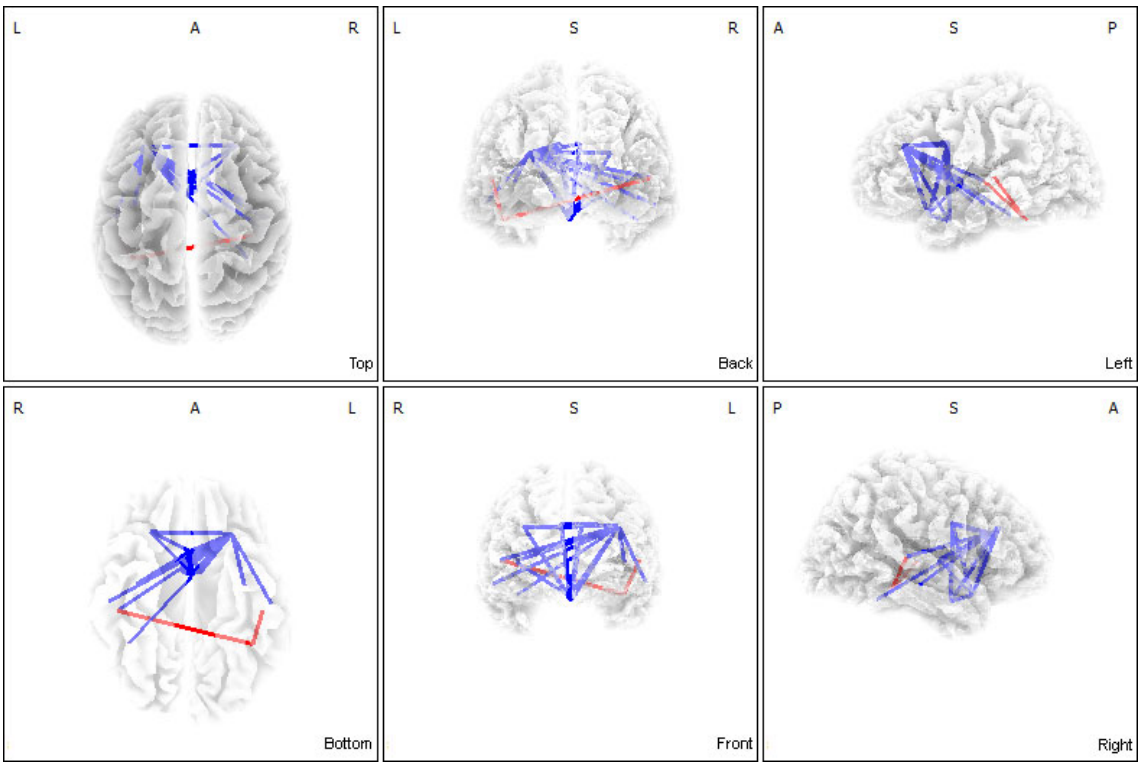


FIG. 4. Connectivity contrast analysis between between tinnitus patients and control group ($P < 0.05$). Decreased phase-lagged gamma (30–45 Hz) synchronization for tinnitus patients is found, except for increased phase-lagged gamma (30–45 Hz) synchronization between the left parahippocampal area, the left and right auditory cortex. L, left; R, right; A, anterior; P, posterior; S, superior.

continuity, filling in missed auditory input, as unconscious sensory repair for missed speech occurs in Broca's area, bilateral anterior insula and pre-SMA (Shahin *et al.*, 2009). This is in accordance with a PET study of tinnitus (Mirz *et al.*, 2000) which found a right prefrontal–temporal network subserving tinnitus perception. In chronic tinnitus theta activity is increased in the lower part of the premotor cortex. This might be related to tonal memory which in fMRI is related to activation of the lower premotor cortex (encroaching on Broca's area), the auditory cortex, the inferior parietal lobe and the anterior insula. As in chronic tinnitus the auditory cortex and the anterior insula are also more activated in comparison to tinnitus of recent onset this could suggest that chronic tinnitus is mediated by similar areas to those implicated in tonal memory.

### *Dorsal anterior cingulate cortex and insula*

Our result also revealed that the dorsal anterior cingulate cortex (dACC) and insula become more involved over time. An explanation cannot be given yet for their involvement but a hypothesis can be proposed.

Whether an auditory stimulus is perceived consciously or not depends on fluctuations in the dACC and insula (Sadaghiani *et al.*, 2009), analogous to what has been described for pain (Boly *et al.*, 2007). The dACC plus anterior insula are thought to be part of the salience network (Seeley *et al.*, 2007), encoding behaviourally important and functionally significant inputs. Thus it is plausible that dACC and anterior insula signify a lack of habituation to the constant phantom sound, analogous to what has been described for pain (Mobascher *et al.*, 2010). These results have to be seen in the light of connectivity.

### *Connectivity*

Both decreased and increased connectivity were found in tinnitus patients in comparison to control subjects between the different ROIs for theta, alpha and gamma activity. For the theta frequency band, increased connectivity was demonstrated between the left and right parahippocampal areas. For the alpha2 frequency band, increased connectivity was found between the left parahippocampal area and the left auditory cortex, and between the right parahippocampal area and the right auditory cortex. Increased connectivity was also revealed within the gamma frequency band between the left parahippocampal area and the left and right auditory cortex for tinnitus patients in comparison to control subjects. Previous research has already demonstrated that a direct connection between the auditory cortex and the parahippocampal area is necessary for auditory sensory gating (Grunwald *et al.*, 2003; Boutros *et al.*, 2005, 2008; Korzyukov *et al.*, 2007). With respect to tinnitus, patients showed a pattern of decreased functional connectivity indicating that there are fewer connections formed within the brain, similar to the findings obtained with MEG (Schlee *et al.*, 2009).

Chronic tinnitus in comparison to tinnitus of recent onset goes along with a decrease in theta and alpha connectivity, as well as a decrease in gamma connectivity. However, there is also an increase in gamma connectivity between left parahippocampal cortex, left auditory cortex, left insula and right DLPFC. A recent MEG study has indicated decreased connectivity in the alpha frequency band together with an increase in gamma-band connectivity for longer lasting tinnitus (> 4 years; Schlee *et al.*, 2009). The connections between DLPFC, primary and secondary auditory cortex are interesting, as are those between the insula and the primary and secondary auditory cortex. In addition, reduced gamma phase-lagged connectivity was also found between the left primary and secondary auditory cortex and the left

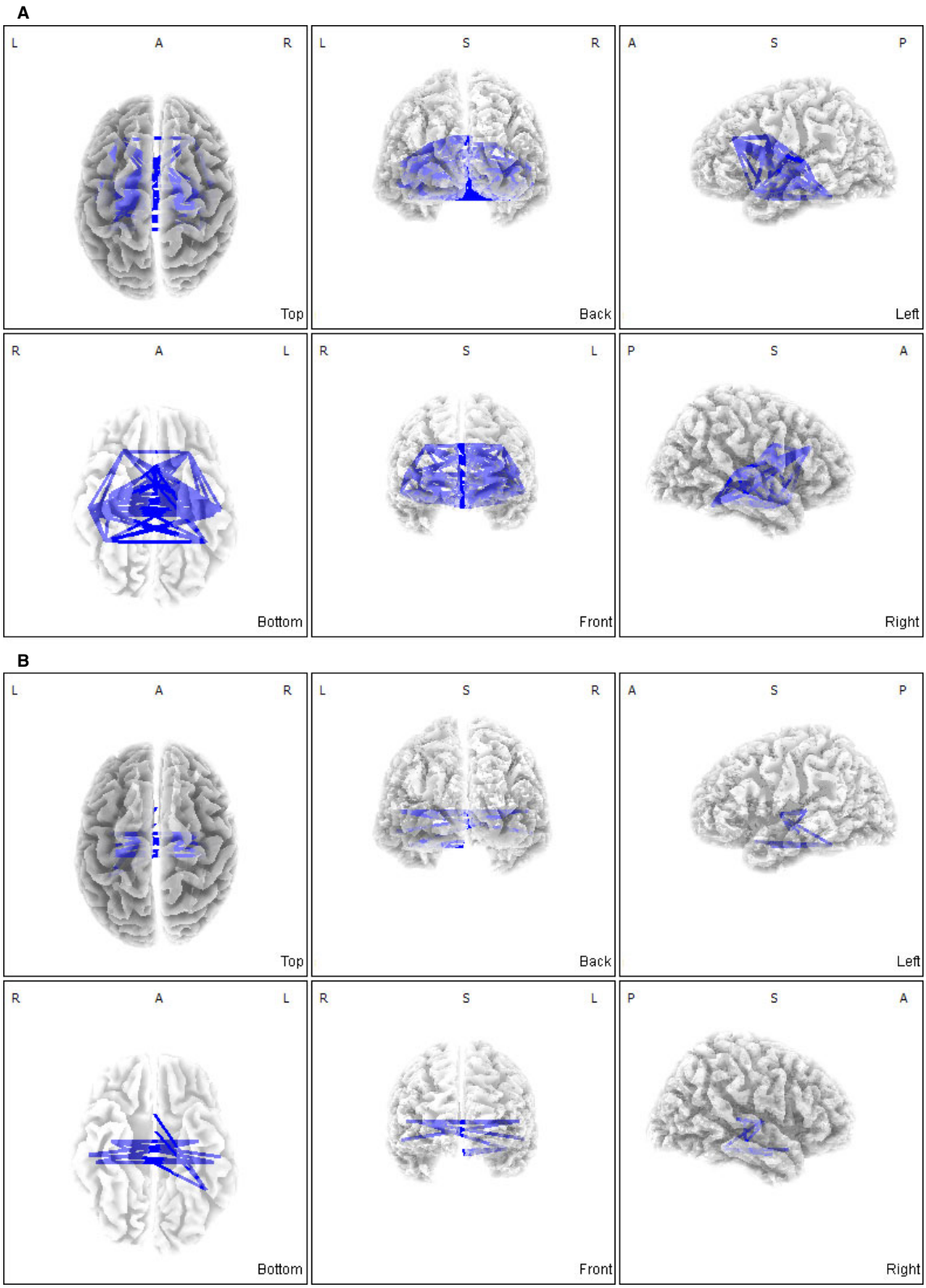


FIG. 5. Connectivity contrast analysis between chronic tinnitus patients and tinnitus patients with recent onset ($P < 0.05$). Decreased (A) theta (4–7.5 Hz) and (B) alpha2 (10–12 Hz) connectivity for chronic tinnitus patients. L, left; R, right; A, anterior; P, posterior; S, superior.

parahippocampal area. This is also in accordance with the findings of Schlee *et al.* (2009) who argue that the left temporal lobe shows a major hub in patients with short tinnitus duration, but this decreases with longer tinnitus duration.

As mentioned before, the involvement of the parahippocampal area in the network might be responsible for constantly updating the tinnitus, preventing habituation (De Ridder *et al.*, 2006) due to its sensory gating function, which has been shown in both animals

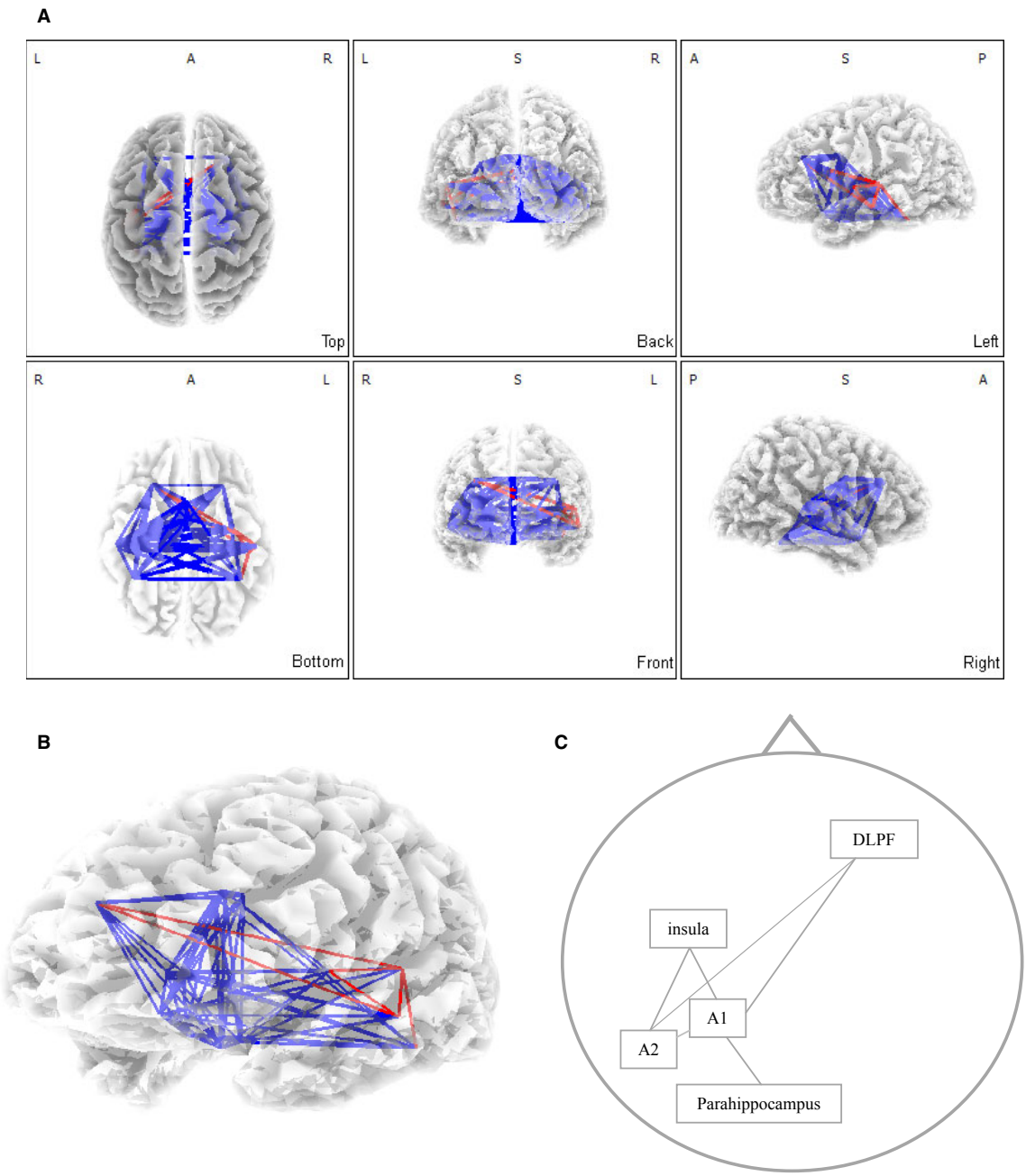


FIG. 6. Connectivity contrast analysis between chronic tinnitus patients and tinnitus patients with recent onset ($P < 0.05$). Decreased gamma (30–45 Hz) connectivity is noted, except for increased gamma (30–45 Hz) connectivity between the parahippocampal area and A1, between the primary and secondary auditory cortices, and between the auditory cortices and the insula as well as the DLPFC, for chronic tinnitus patients. L, left; R, right; A, anterior; P, posterior; S, superior. (A) General overview, (B) 3-D view, (C) schematic overview.

(Bickford *et al.*, 1993) and humans (Boutros *et al.*, 2008). The connection between the insula and the auditory areas might be in charge of allocating persistent attention to the tinnitus and therefore maintaining the tinnitus in consciousness (Bamiou *et al.*, 2003).

### *Limitation*

Although previous research has shown that EEGs performed with only 19 electrodes are capable of source localization, increasing the number of electrodes to 32 or 64 might refine the source localization and functional connectivity measures. Therefore further research is needed to confirm these findings using EEG systems with more electrodes as well as using other imaging techniques (i.e. fMRI, PET etc.).

## Conclusion

In summary, the generators involved in tinnitus of recent onset seem to change over time with increased activity in several brain areas. This is associated with a decrease in connectivity between the different auditory and nonauditory brain areas, with the exception of an increase in gamma-band connectivity between the left parahippocampal area, left primary and secondary auditory cortex, and the left insula and right DLPFC.

## Supporting Information

Additional supporting information can be found in the online version of this article:

Fig. S1. Split-half connectivity contrast analysis between chronic tinnitus patients and tinnitus patients with recent onset ($P < 0.05$). Decreased (a) & (b) theta (4–7.5 Hz) connectivity for chronic tinnitus patients.

Fig. S2. Split-half connectivity contrast analysis between chronic tinnitus patients and tinnitus patients with recent onset ($P < 0.05$). Decreased (a) & (b) alpha 2 (10–12 Hz) connectivity for chronic tinnitus patients.

Fig. S3. Split-half connectivity contrast analysis between chronic tinnitus patients and tinnitus patients with recent onset ($P < 0.05$). Decreased (a) & (b) gamma (30–45 Hz) connectivity for chronic tinnitus patients.

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## Abbreviations

BA, Brodmann area; dACC, dorsal anterior cingulate cortex; DLPFC, dorsal lateral prefrontal cortex; EEG, electroencephalographic or electroencephalography; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalograpic or magnetoencephalography; MNI, Montreal Neurological Institute; ROI, region of interest; rTMS, repetitive transcranial magnetic stimulation; sLORETA, standardized low-resolution brain electromagnetic tomography.

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