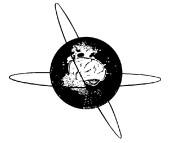




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Involvement of cortico-subcortical circuits in normoacoustic chronic tinnitus: A source localization EEG study

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HIGHLIGHTS

- We used sLORETA to study the cerebral activity in normoacoustic tinnitus sufferers.
- EEG sources were decreased in left temporal and inferior parietal gyri in patients.
- Cortico-thalamo-cortical circuits can be involved without thalamic deafferentation.

ABSTRACT

Objective: To better characterize brain circuits dysfunctions in normoacoustic tinnitus sufferers.**Methods:** 17 normoacoustic chronic, unilateral high-pitched tinnitus sufferers (6 females, 43.6 ± 9.8 y.o., disease duration 22 ± 35 months) underwent a 29-channel resting-state electroencephalography (EEG – 5 min opened-eyes, 5 min closed-eyes) and auditory oddball paradigm for event-related potentials analyses (ERPs – N1, P2 and P300). Cortical 3D distribution of current source density was computed with sLORETA. Results were compared with 17 controls (9 females, 45.7 ± 15.1 y.o.).**Results:** Eyes opened, tinnitus sufferers had lower alpha and beta sources in the left inferior parietal lobule. Eyes closed, tinnitus sufferers had decreased alpha sources in the left inferior temporal and post-central gyri, and low gamma sources in the left middle temporal gyrus. EEG data did not correlate with tinnitus sufferers' clinical features. Subjects with tinnitus had shorter N1 and P2 latencies. P300 did not differ between groups. sLORETA solutions showed decreased sources of these ERPs in the left inferior temporal gyrus in the tinnitus group.**Conclusions:** We showed cortico-thalamo-cortical involvements in normoacoustic tinnitus with hyperexcitability of the left auditory cortex and inferior temporal gyrus.**Significance:** This might reflect processes of maladaptive cortical plasticity and memory consolidation. Further validation is needed to establish the value of this tool in customizing therapeutic approach.

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1. Introduction

According to one of the most widely accepted definitions, subjective tinnitus is “the perception of sound that results exclusively from activity within the nervous system without any corresponding mechanical, vibratory activity within the cochlea, and not related to external stimulation of any kind” (Jastreboff, 1995). Tinnitus is a common symptom, perceived chronically by

10–15% of the general population, and 10–20% of these subjects report interference in their everyday life (Leske, 1981; Quaranta et al., 1996).

The underlying physiological mechanisms of tinnitus are largely unknown, but as Kaltenbach mentioned, “the expectation is associated with changes of activity that normally occur only when sound is present... the most likely candidates are changes in spontaneous neural activity that simulate sound-elicited activity” (Kaltenbach, 2011). Recent converging evidences suggest that the tinnitus-related neural activity is more complex and can be provoked or modulated by inputs from somatosensory, somatomotor and visual-motor system (Rocha and Sanchez, 2007; Sanchez et al., 2007; Sanchez and Rocha, 2011).

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Electroencephalographic (EEG) studies in tinnitus have highlighted several abnormalities regarding the background cerebral oscillations in various frequency bands, such as theta, delta, alpha, beta or gamma. Although previous EEG or magnetoencephalographic (MEG) studies on tinnitus sufferers reported conflicting data, a general tendency is a concentration of abnormalities mainly over the temporo-parietal (Shulman and Goldstein, 2002; Shulman et al., 2006; Schlee et al., 2009; Moazami-Goudarzi et al., 2010) and frontal regions (Shulman and Goldstein, 2002; Shulman et al., 2006). Details on the topographic distribution of EEG changes have been provided by 3-D based analyses, revealing abnormalities in current source density distribution, primarily over the auditory areas and insular cortex (Moazami-Goudarzi et al., 2010) as well as frontopolar, Posterior Cingulate Cortex (PCC) and the parahippocampal area (Vanneste et al., 2010a).

The lack of consistency among the different studies might be linked, at least partially, to clinical factors such as the presence of peripheral auditory disorders, medication, level of distress, etiology. In particular, the investigation of brain circuits associated with tinnitus in normoacoustic subjects is of interest since it could help dissociating the impairments due to the auditory loss, from the impairments due to the central mechanisms of tinnitus. As a consequence, the present study aimed at assessing the level of involvement of different brain circuits in normoacoustic tinnitus sufferers. To this aim, we used EEG to study and localize resting-state activity in a wide frequency range (0.5–60 Hz) as well as auditory and cognitive event-related potentials (ERPs). The interest of this kind of approach would be to help customize future treatment plans on an individual basis, especially for repetitive transcranial magnetic stimulation (rTMS).

2. Methods

2.1. Participants

Seventeen consecutive tinnitus sufferers (6 females, 11 males, mean age \pm SD: 43.4 ± 9.8 years, mean disease duration: 22 ± 35 months, 6 subjects presented with a right-sided tinnitus) with chronic tinnitus were analyzed in the period of January 2009–January 2013 within outpatients referred to the “Tinnitus Centre” of the San Raffaele Hospital. All of them reported a tinnitus which was audible all days for at least 6 months. MRI, EEG, brainstem auditory evoked potentials were also performed as part of their diagnostic routine for the exclusion of neurological disorders, including epilepsy, or peripheral auditory damage. Tinnitus sufferers were selected if they referred the presence of unilateral tinnitus, and if: (a) they presented a hearing threshold <15 dB Hearing Level for frequencies between 125 and 8000 Hz (pure tone audiometry was performed with a precision of a half octave); (b) audiometric exam demonstrated no gap >5 dB between the two thresholds in all frequencies; (c) clinical history was negative for a previous hearing loss; (d) brainstem auditory evoked potentials (BAEP) presented normal values; (e) brain magnetic resonance imaging was negative; (f) resting EEG was normal at visual inspection. Exclusion criteria were: (a) history of neurological disorders; (b) ongoing therapies with drugs active on central nervous system, particularly benzodiazepines, Selective Serotonin Reuptake Inhibitors, Calcium Blockers and anti-epileptic drugs (a 15 days wash-out was required). All subjects reported a high pitched tinnitus (8 kHz in 7 cases, 6 kHz in 9 and 4 kHz in the remaining 3). Five of them presented hyperacusis.

Tinnitus pitch and the following other psychoacoustic measurements were obtained for each tinnitus sufferer (data are presented in Table 1): Loudness (L), Loudness Discomfort Level (LDL), Minimum Masking Level (MML) and Residual Inhibition (RI).

Furthermore, they were asked to complete the Tinnitus Handicap Inventory (THI) questionnaire and a Visual Analogue Scale (VAS) for the level of tinnitus annoyance, on a scale between 0 (no annoyance) to 100 (highest annoyance ever).

Tinnitus pitch was approached gradually by presenting successive pairs of tones in the unaffected ear from which the subjects selected the tone that was closest to the tinnitus pitch. Loudness was determined by balancing the loudness of tinnitus with the loudness of a tone at pitch frequency in the contralateral ear and was expressed in decibel sensation level (SL). MML has been determined using broadband noise; monoaural hearing threshold was obtained first, then volume was raised until the subject reported that the tinnitus was inaudible. Both L and MML were determined using a 1 dB step-size. LDL was defined as the mean loudness level intolerance for frequencies between 250 and 8000 Hz. For the assessment of RI (expressed in seconds), subjects were presented with a white noise in the affected ear at an intensity of 10 dB higher than the MML for 1 min (Mitchell et al., 1993). The validated THI, developed by Newman and Jacobson (Newman et al., 1996), is a 25-item self-administered questionnaire, divided into functional, emotional, and catastrophic subcategories. Tinnitus sufferers' clinical data are reported in Table 1.

Data were compared with 17 normoacoustic control subjects without tinnitus (9 females, 8 males, mean age \pm SD: 45.7 ± 15.1 years). Controls presented the same exclusion criteria as tinnitus sufferers. Participants gave their written informed consent before participating to the study which was approved by the San Raffaele Scientific Institute Ethics Committee.

2.2. EEG recording

Subjects were seated in a comfortable armchair, in a quiet room. Recordings consisted in 10 min of resting EEG, 5 min eyes closed and 5 min eyes opened. Both conditions were studied in order to control for the alpha contamination usually observed in the eyes closed. Resting-state EEG was followed by an auditory oddball paradigm in which 2 tone bursts were binaurally presented through headphones in a random order. One of the 2 stimuli (frequent, 1000 Hz) represented 80% of the stimuli, and the second one (rare, 2000 Hz) represented 20% of the tones, for a total of 330 stimuli. Subjects were asked to pay attention to the rare stimuli. EEG was recorded using 29 scalp electrodes mounted on an elastic cap (Electro-cap International, Eaton, OH, USA) according to the 10-20 International system, with binaural reference and bipolar electro-oculogram monitoring using a commercial equipment (Synamps amplifiers and Scan 4.3, Neuroscan Inc., Herndon, VA, USA), filtered (DC to 50 Hz), and digitized at 250 Hz sampling frequency. Electromyographic (EMG) activity of bilateral extensor carpi radialis (ECR) muscles was recorded in order to monitor subjects' complete relaxation during recordings. EMGs were acquired using Ag/AgCl surface electrodes in a bipolar montage. EEG and EMG impedances were kept below 10 k Ω .

2.3. Data analyses

EEGs were analyzed using BrainVision Analyzer 2.0 (Brain Products GmbH, Munich, Germany). Data were first re-referenced against the average reference. Gross artifacts were manually removed from the raw EEGs after visual inspection, while ocular artifacts were corrected using an ICA-based correction process (Iriarte et al., 2003) using a value trigger algorithm to detect blinks. Blinks were thus detected on their absolute values on the EEG traces. The definitive blinks were ascertained by means of a correlation method. The ICA algorithm used was an Infomax restricted algorithm. For resting-state analyses, traces were segmented in at least 30 2 s-epochs. Spectra of each epoch were calculated by

Table 1

Tinnitus sufferers' clinical data. Gender and age are reported as well as the clinical scores during tinnitus evaluation. MML: Minimum Masking Level; RI: Residual Inhibition; VAS: Visual Analogue Scale; THI: Tinnitus Handicap Inventory; S.D.: Standard Deviation.

Patient	Gender	Age (y)	Tinnitus description											
			Laterality	Duration (months)	Loudness (dB SL)	MML (dB SL)	RI (s)	VAS Annoyance	VAS Intensity	THI total score	THI Functional	THI Emotional	THI Catastrophic	Pitch (kHz)
1	M	45	R	2	4	7	0	40	50	28	4	14	10	4
2	M	53	R	24	3	4	20	40	30	32	14	4	14	6
3	F	54	L	46	9	9	0	70	80	50	22	14	14	1
4	M	37	L	2	9	12	25	70	80	72	38	20	14	6
5	M	32	L	12	8	11	0	60	80	46	16	14	16	8
6	M	41	R	4	6	8	3	85	80	62	20	30	12	White noise
7	M	35	L	2	4	6	10	45	50	60	28	18	14	8
8	M	45	R	144	7	11	0	55	50	56	24	20	12	6
9	F	47	L	6	5	7	12	35	45	40	20	8	12	6
10	F	59	R	48	3	4	30	50	50	32	20	4	8	6
11	M	34	L	8	3	4	20	30	24	26	10	2	14	6
12	F	48	L	20	13	19	0	96	100	96	44	32	20	8
13	F	19	L	7	4	7	15	65	50	46	30	4	12	6
14	M	47	L	2.5	9	21	0	75	80	72	34	28	10	8
15	M	48	L	14	9	20	20	80	65	54	20	16	18	8
16	M	44	R	2	4	9	5	40	50	34	10	14	10	6
17	F	53	L	36	9	16	0	100	85	80	42	26	12	White noise
Average				43.6										
S.D.				9.8										
				22.32	6.41	10.29	9.41	60.94	61.71	52.12	23.29	15.76	13.06	
				34.90	2.96	5.59	10.37	21.55	21.24	19.84	11.42	9.48	3.01	

fast Fourier transform (FFT), with a frequency resolution of 0.5 Hz, tapered by a Hanning window. Spectra were then averaged across all epochs in order to compute a mean power spectrum for each electrode. The frequency bands of interest were: delta (1.5–6 Hz), theta (6.5–8 Hz), alpha 1 (8.5–10 Hz), alpha 2 (10.5–12 Hz), beta 1 (12.5–18 Hz), beta 2 (18.5–21 Hz), beta 3 (21.5–30 Hz), and low gamma (30.5–60 Hz). For each electrode, all these spectra values were normalized according to the whole spectra power (1.5–60 Hz) of the same electrode. This information was used to produce relative power scalp maps and to perform a preliminary evaluation of inter-group differences.

For source localization, the 2 s-epochs (before FFT analyses) were exported for sLORETA calculation. For ERP analyses, EEG was filtered at 0.03–30 Hz, and segmented in 850 ms-epochs (from –50 ms to +800 ms to the tone stimulus). Epochs were then averaged according to the “rare” and “frequent” conditions. N100, P200, and P300 peak amplitudes and latencies were then obtained from the electrode displaying the greatest ERP.

The sLORETA software (R.D. Pascual-Marqui, Key Institute for Brain-Mind Research, Zurich) was used to compute the cortical three-dimensional (3D) distribution of current density for the resting state EEG and ERPs (Pascual-Marqui, 2002). EEG epochs were directly imported and processed; the re-referencing and spectral calculations (resting state) were performed by the software. For the resting state conditions, cross spectrums of the 2 s-artifact-free epochs were obtained, for every subject, for the following frequency bands: delta (1.5–6 Hz), theta (6.5–8 Hz), alpha 1 (8.5–10 Hz), alpha 2 (10.5–12 Hz), beta 1 (12.5–18 Hz), beta 2 (18.5–21 Hz), beta 3 (21.5–30 Hz), and low gamma (30.5–60 Hz). For ERP analyses, the time windows were set to cover the ranges of peak latencies of each subject. For N1 analyses, windows of 80–140 ms post stimulus were used; for P2 analyses we used 170–270 ms time windows and 280–400 ms post stimulus windows were used of the P300 analyses. The sLORETA method is a standardized discrete, 3D distributed, linear, minimum norm inverse solution (Pascual-Marqui, 2002). 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. The intracerebral volume was partitioned in 6239 voxels at 5 mm spatial resolution. Thus, sLORETA images represent the standardized electric activity at each voxel in neuroanatomic Montreal Neurological Institute (MNI) space as the exact magnitude of the estimated current density. Anatomical labels are reported using MNI space, with correction to Talairach space. In order to reduce intersubject variability, for each subject, sLORETA values at each voxel were normalized with the power density averaged across all frequencies (0.5–60 Hz) and across all voxels of the volume (Caso et al., 2012).

2.4. Statistical analyses

Magnitude of tinnitus (VAS annoyance, VAS intensity, MML, loudness and THI total) was compared between left- and right-sided tinnitus sufferers using Mann–Whitney test for independent samples (due to the sample size). Comparisons of P300 peak amplitude and latency between groups were performed using independent-samples *t*-test or a Mann–Whitney test, depending on the normality of the data distribution, as evaluated by the Kolmogorov–Smirnov test. N100 and P200 peak amplitudes and latencies were compared between groups using either an ANOVA for repeated measures, or the Conover's free distribution method, a non-parametric ANOVA based on ranks (Conover and Iman, 1982), depending on the data distribution. Two main factors were used: CONDITION (2 levels: rare and frequent) and GROUP (2 levels: tinnitus sufferers and controls). In order to perform a pre-statistical analysis of relative spectra power between groups, data were pooled in regions of interest (ROIs). Each ROI was calculated as the average of the spectra of the concerned electrodes, for each frequency band. Ten ROIs were considered: Frontal left-FI (FP1, F3, F7), Frontal right-Fr (FP2, F4, F8), Fronto-central-Fc (Fz, FCz), Central left-CI (FC3, C3), Central right-Cr (FC4, C4), Centro-parietal-CP (Cz, CPz, Pz), Temporal left-TI (T3, T5, TP7, FT7), Temporal right-Tr (T4, T6, TP8, FT8), Parietal left-PI (CP3, P3, O1), and Parietal right-Pr (CP4, P4, O2). Data were compared using *t*-tests for independent variables or Mann–Whitney test in case of non-parametric values. FFT data between left-sided and right-sided tinnitus sufferers were compared using Mann–Whitney tests.

Data were considered significant when $p < 0.05$. These statistical analyses were performed with SPSS/PC+ 13.0 (SPSS Inc., Chicago, IL). Cross-sectional and longitudinal correlations between tinnitus sufferers' clinical data and maximal current source density were assessed using Pearson or Spearman tests, according to the data distribution.

The sLORETA software package was used to perform the statistical comparisons of sLORETA source localization between groups. The methodology used is non-parametric. It is based on estimating, via randomization, the empirical probability distribution for the max-statistic (e.g. the maximum of a t or an F statistic), under the null hypothesis. This methodology corrects for multiple testing (i.e., for the collection of tests performed for all electrodes and/or voxels, and for all time samples and/or discrete frequencies). Due to the non-parametric nature of the method, its validity need not rely on any assumption of Gaussianity (Nichols and Holmes, 2002). This method was also used to compare left-sided versus right-sided tinnitus sub-groups.

3. Results

VAS annoyance, VAS intensity, MML and THI total did not differ between left- and right-sided tinnitus sufferers ($p = 0.256$, 0.126 , 0.149 and 0.122 , respectively). Only the loudness differed between the two groups ($p = 0.048$), left-sided sufferers reporting louder tinnitus.

Regarding resting state analyses, relative power maps are shown in Fig. 1. In the open eyes condition, tinnitus sufferers had significantly less alpha 2 power compared with controls in the parietal areas bilaterally (left: $p = 0.002$, right: $p = 0.026$). There was also an important significant reduction of beta 2 ($p = 0.014$) and beta 3 power ($p = 0.026$) in the tinnitus group compared to controls over the left temporal area. Conversely, there were no significant differences between tinnitus sufferers and controls for the delta, theta, alpha 1, beta 1 and low gamma rhythms ($p > 0.05$).

In the closed eyes condition, there was a significant decrease of alpha 2 power in the tinnitus group compared to controls in the centro-parietal and left temporal regions ($p = 0.045$ and $p = 0.041$, respectively). There was also a significant decrease of low gamma power in the left frontal and parietal areas ($p = 0.035$ and $p = 0.001$, respectively).

The statistical maps comparing sLORETA solutions between tinnitus sufferers and controls confirmed the preliminary FFT analyses at the sensor level and showed, in the open eyes condition, significant lower sources of the alpha 2 (10.5–12 Hz), beta 2 (18.5–21 Hz) and beta 3 (21.5–30 Hz) rhythms in the left inferior parietal lobule (BA 40) in the tinnitus' group (Fig. 2). Alpha 2 had also lower CSD in the left middle occipital gyrus (BA 19) in the tinnitus group, compared to controls.

Eyes closed, tinnitus sufferers had significantly decreased alpha 2 sources in the left inferior temporal and post-central gyri (BA 37 and BA3), and low gamma sources in the left middle temporal gyrus (BA 39) (Fig. 3). Such decreased activity did not correlate with tinnitus sufferers' clinical features.

P300 was observed at a mean peak latency of 342.4 ± 25.2 ms (mean \pm SD), and a mean peak amplitude of 15.4 ± 1.4 μ V in the control group, and at 353.5 ± 5 ms and 15.9 ± 0.9 μ V in the tinnitus group (Fig. 4A). These values did not differ significantly between groups ($p = 0.762$). Statistical maps of sLORETA solutions individuated a significant lower activity in the left auditory cortex (BA22 and BA42) (Fig. 4B).

Regarding the analyses of the N100 latency, the CONOVER showed a significant effect of the main factor GROUP ($F_{1,33} = 4.26$, $p = 0.048$) and a tendency for a CONDITION effect ($F_{1,33} = 3.85$, $p = 0.059$), demonstrating shorter latencies in the tinnitus group (Table 2). For the P200 latency, the CONOVER revealed a significant effect of the main factor CONDITION ($F_{1,33} = 37.57$, $p < 0.001$) and no group effect. The P200 latency was indeed shorter in the "rare" condition, in both groups (Table 2). The CONOVER analysis of the N100 peak amplitude showed a significant CONDITION effect ($F_{1,33} = 4.4$, $p = 0.023$) and no significant GROUP effect ($p = 0.132$),

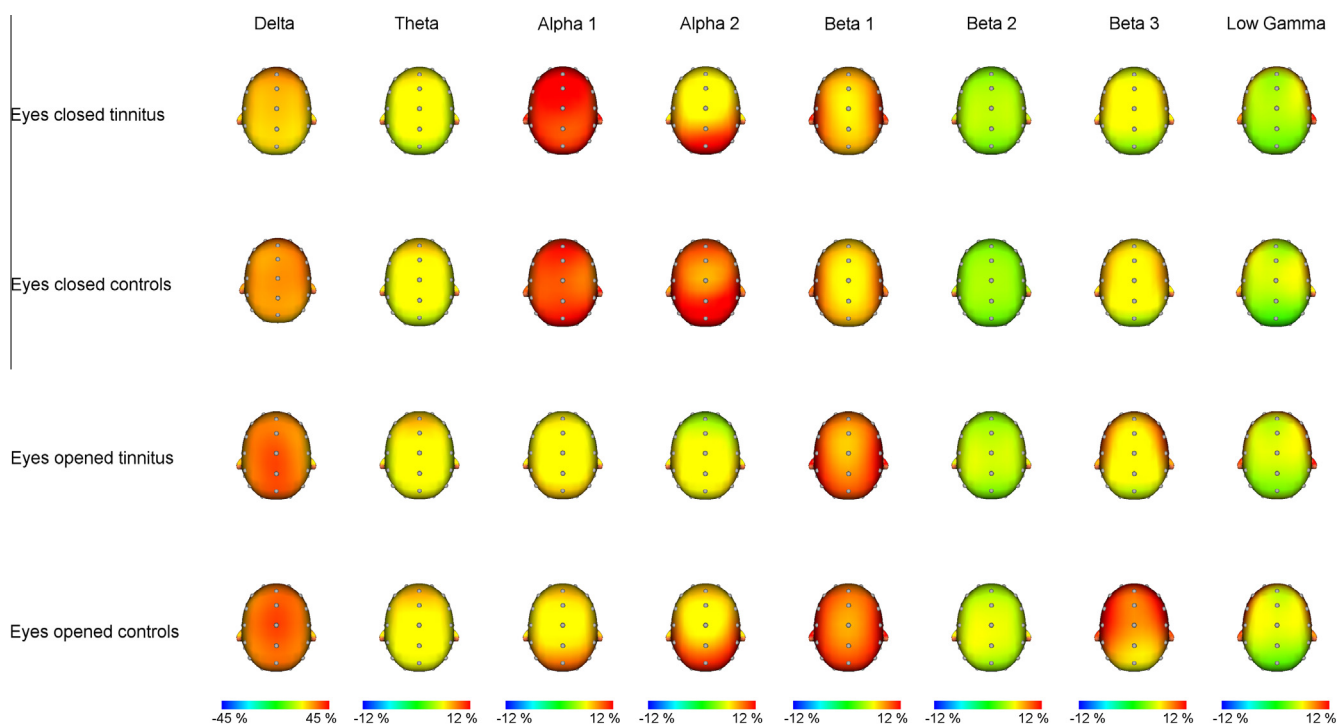


Fig. 1. Grand average of the relative FFT power maps in tinnitus sufferers and controls, for each frequency band of interest (delta: 1.5–6 Hz, theta: 6.5–8, alpha 1: 8.5–10, alpha 2: 10.5–12, beta 1: 12.5–18, beta 2: 18.5–21, beta 3: 21.5–30, low gamma: 30.5–60). For each sensor, values are expressed as percentages of the global spectra power (1.5–60 Hz) of the same sensor.

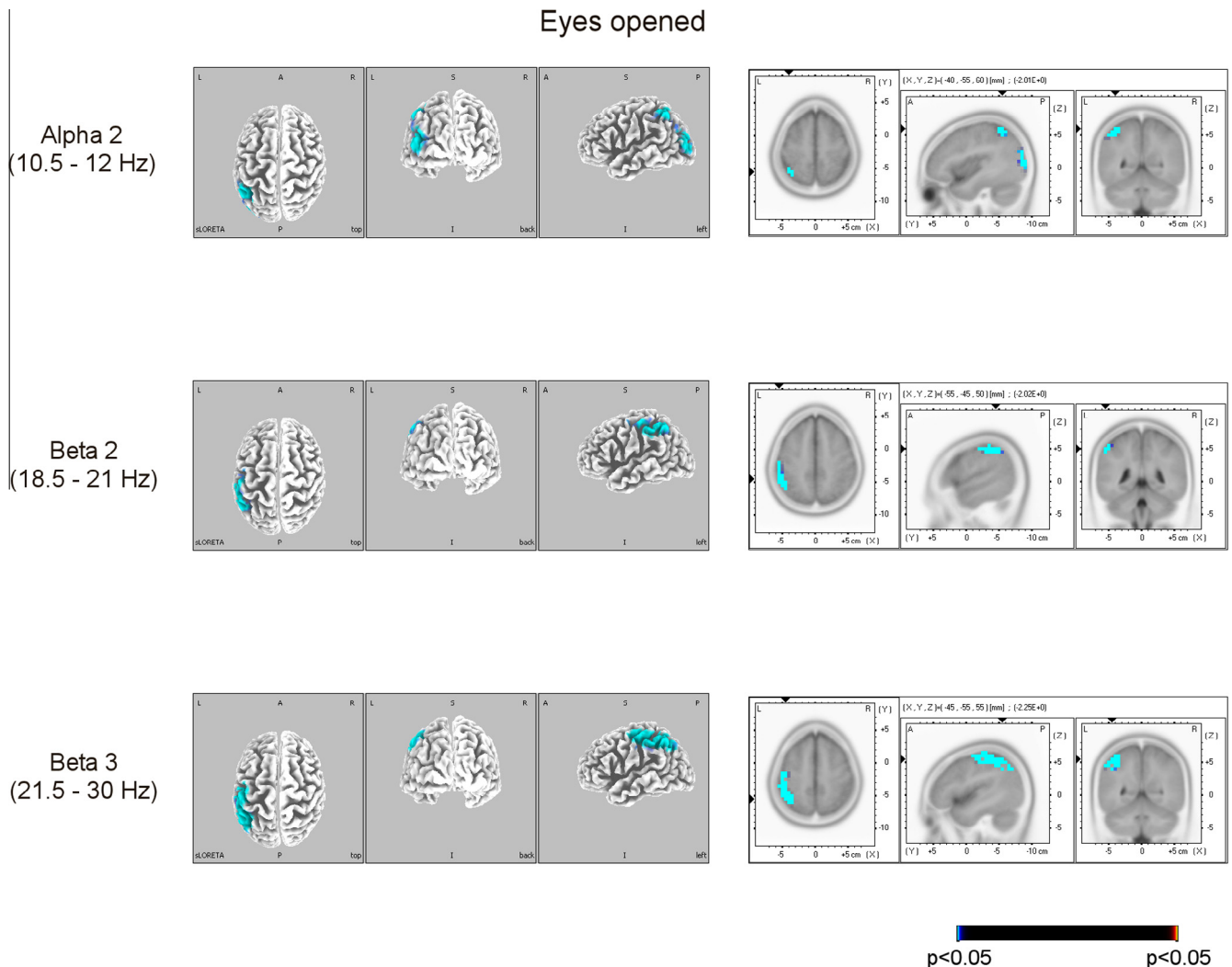


Fig. 2. Grand average of the statistical maps comparing sLORETA solutions between tinnitus sufferers and controls, eyes opened. Data showed significant lower sources of alpha 2 (10.5–12 Hz), beta 2 (18.5–21 Hz) and beta 3 (21.5–30 Hz) rhythms in the left inferior parietal lobule (BA 40) in the tinnitus group.

demonstrating greater N100 in the frequent condition, for both groups. Conversely, the peak amplitude of the P200 did not differ between groups ($p = 0.069$) and conditions ($p = 0.608$).

The sLORETA analyses related to the N1/P2 analyses showed a significant lower cortical source in the left inferior temporal gyrus (auditory cortex, BA21) in the tinnitus group in both stimulus conditions (rare and frequent) (Fig. 5).

FFT and sLORETA analyses showed no significant differences between the left-sided and right-sided tinnitus subgroups, either in the open eyes, or in the closed eye condition ($p > 0.05$ for all the frequency bands, in the two conditions).

4. Discussion

The main findings of the present study revealed decreased current density in the left inferior temporal and parietal cortical sources of the alpha, beta and gamma rhythms in tinnitus sufferers. Surprisingly, few studies have been investigating resting oscillatory activity in tinnitus, with highly variable results, showing decreased (Weiler et al., 2000; Shulman and Goldstein, 2002; Weisz et al., 2005, 2007), increased (Moazami-Goudarzi et al., 2010; Adjamian et al., 2012; Pawlak-Osińska et al., 2013; Vanneste et al., 2013) or no significant changes (Balkenhol et al., 2013) of cortical activity in the frequency ranges mainly from 0.5 to 60 Hz. Our results are consistent with some previously reported

findings (Weiler et al., 2000; Shulman and Goldstein, 2002; Weisz et al., 2005, 2007) and reinforce the hypothesis of a dysfunction in the thalamo-cortical loops in tinnitus sufferers (Llinás et al., 1999, 2005). Indeed, alpha, beta and gamma oscillations reflect the activity of thalamo-cortical circuits highly involved in sensorimotor functions (Pfurtscheller, 1981; Steriade and Llinás, 1988; Pfurtscheller and Neuper, 1992; Neuper and Pfurtscheller, 1996). Tinnitus would reflect an integrated interneuronal neurotransmission pathway including the frontal, temporal, and parietal lobes, thalamus, and cerebellum (Shulman, 2005). A major hypothesis on the pathophysiological mechanisms is that tinnitus would involve a lesion leading to deafferentation of excitatory inputs on thalamic relay cells (Tonndorf, 1987; Möller, 1997; Lockwood et al., 1998). This would lead to a thalamic deactivation (Llinás et al., 2005), disrupting in turn thalamo-cortical interactions (Jeanmonod et al., 1996; Llinás et al., 1999), and leading to the appearance of tinnitus. The role of thalamus in tinnitus pathophysiology has been previously discussed by several authors. Thalamic abnormalities in tinnitus sufferers have been widely reported in both structural (Mühlau et al., 2006) and functional (Mirz et al., 1999) studies, and it has been suggested, from EEG or MEG studies, that tinnitus would result from thalamo-cortical dysrhythmia (Llinás et al., 1999; Moazami-Goudarzi et al., 2010).

Decreased current source densities of alpha and beta rhythms would imply an increased activity of the involved areas

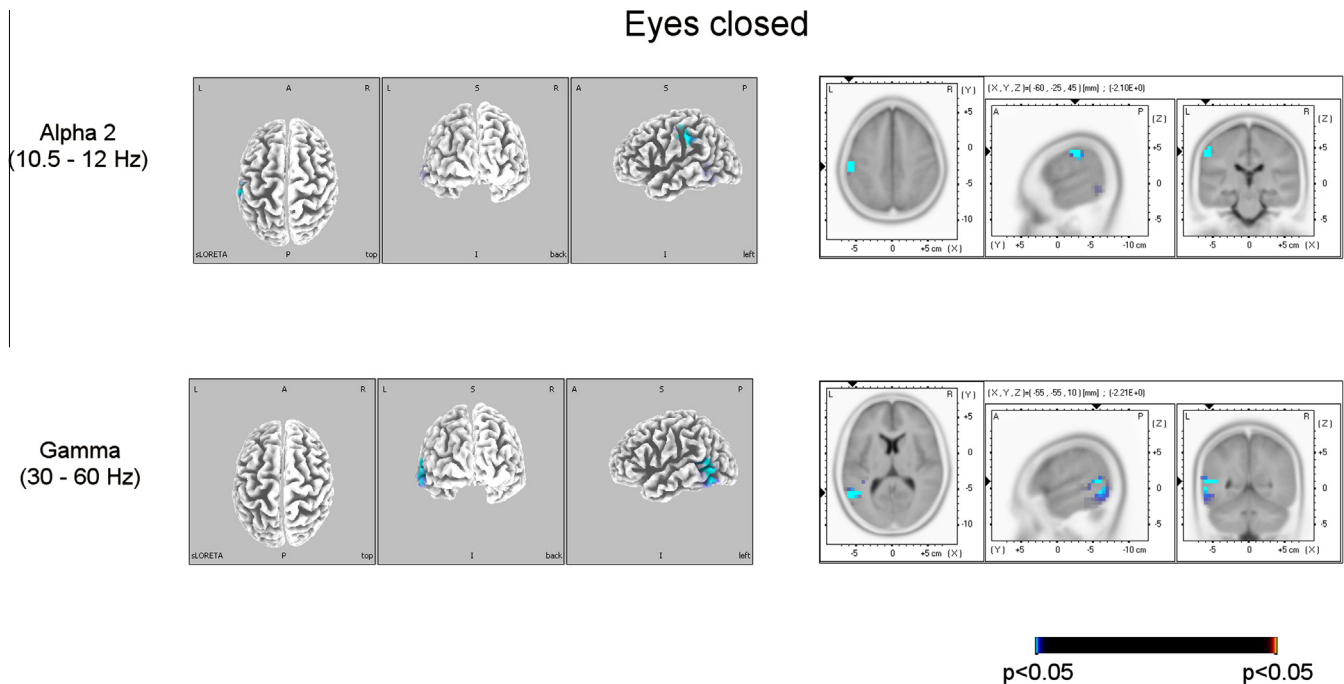


Fig. 3. Grand average of the statistical maps comparing sLORETA solutions between tinnitus sufferers and controls, eyes closed. Data showed significantly decreased alpha 2 sources in the left inferior temporal and post-central gyri (BA 37 and BA3), and low gamma sources in the left middle temporal gyrus (BA 39) in the tinnitus group.

(Pfurtscheller and Lopes da Silva, 1999), suggesting a hyperactivation of the left parietal and inferior temporal gyri, paralleled by an abnormal gamma activity over the middle temporal lobules in our tinnitus sufferers. Alpha and beta impairments reinforce the hypothesis of an increased cortical excitability in tinnitus. Indeed, an imbalance of inhibition and excitation via GABAergic and glutamatergic influences in mediotemporal cortex has been suggested in nuclear medicine imaging (Shulman, 2005). Single-Photon Emission Computed Tomography (SPECT) studies showed a decreased density of benzodiazepine receptors in the medial temporal cortex in tinnitus sufferers (Shulman et al., 1995; Daftary et al., 2004). Moreover, an increased intracortical facilitation, involving glutamatergic interneurons, over the motor cortex has been demonstrated using TMS (Langguth et al., 2005). An indirect proof has also been the demonstration that inhibitory repetitive transcranial magnetic stimulation over the primary auditory cortex could be useful in tinnitus treatment (Eichhammer et al., 2003; De Ridder et al., 2006; Langguth et al., 2006). This latter result, together with the fact that our data showed increased excitability of the auditory cortex even in the absence of stimulus, as it has also been shown in schizophrenic subjects with auditory hallucinations (Kompus et al., 2011), demonstrates the active role of the auditory cortex in tinnitus, even in normoacoustic subjects with normal MRI and no apparent deaf-ferentation. Moreover, although a previous study showed no differences between normoacoustic and hypoacoustic tinnitus sufferers, the dysfunctions of thalamo-cortical circuits involved in our subjects appear less widespread than those reported in hypoacoustic subjects, in terms of cortical areas and frequencies (Moazami-Goudarzi et al., 2010). The impaired activity of the middle and inferior temporal gyri observed in our study is in favor of non-auditory pathways involved in tinnitus and might reflect abnormal sensory integration and memory consolidation processes. Indeed, the inferior temporal gyrus is involved in memory consolidation, visual processing and multimodal sensory integration (Mesulam, 1998). Hyperexcitability of the bilateral inferior temporal gyrus in tinnitus has been reported in EEG, and PET studies (Weiler et al., 2000; Ashton et al., 2007; Pawlak-Osińska et al., 2013; Adamchic et al., 2014; Song et al., 2015). This abnormal activation, confirmed by

our results, might be related to a mechanism of maladaptive memory consolidation and/or abnormal sensory integration (Song et al., 2012). The middle temporal gyrus plays a role in cognitive processes such as face and object recognition, semantic memory as well as multimodal sensory integration (Cabeza and Nyberg, 2000). Increased activation in the left middle temporal gyrus has been previously reported in EEG and PET studies (Vanneste et al., 2010b; Song et al., 2012) in tinnitus sufferers with hearing loss. These data, together with our results, confirm the involvement of the left middle temporal gyrus in tinnitus, even in normoacoustic subjects. However, as opposed with alpha and beta rhythms, gamma oscillations tend to be increased during sensorimotor tasks (Pfurtscheller and Neuper, 1992; Szurhaj et al., 2006). Thus, a decreased gamma power or gamma current source density might reflect a deficient activity of the underlying cortex. Although more studies are needed to better understand the role of gamma oscillations in tinnitus, together with the role of the middle temporal gyrus in the pathophysiology of the disease, one can hypothesize that our results might reflect an abnormal sensory integration processing, even in normoacoustic subjects.

Discrepancies exist between studies reported in the literature regarding the laterality of brain involvement in tinnitus. Indeed, most studies reported bilateral, left-sided or right-sided cortical involvement. Consistent with our results, a meta-analysis of fMRI and PET studies demonstrated a tendency for a majority of left-sided cortical impairment, irrespective of tinnitus side (Song et al., 2012). Conversely, Weisz et al., (2007) showed a significant association between the side of tinnitus and enhanced delta and gamma activity. The authors demonstrated that left-sided tinnitus subjects presented with right-sided increased gamma oscillations, and vice versa. One major difference with Weisz's study and ours resides in the etiology of the tinnitus sufferers. Indeed, it has been demonstrated that delta and gamma increase might be specific of tinnitus subjects with hearing loss (Adjamian et al., 2012). Thus, the differences between Weisz's study and ours might be due to the fact that our subjects were normoacoustic.

The difference we observed between the eyes opened and closed conditions (decreased beta activity with the eyes opened) might be due to the alpha contamination in the eyes closed

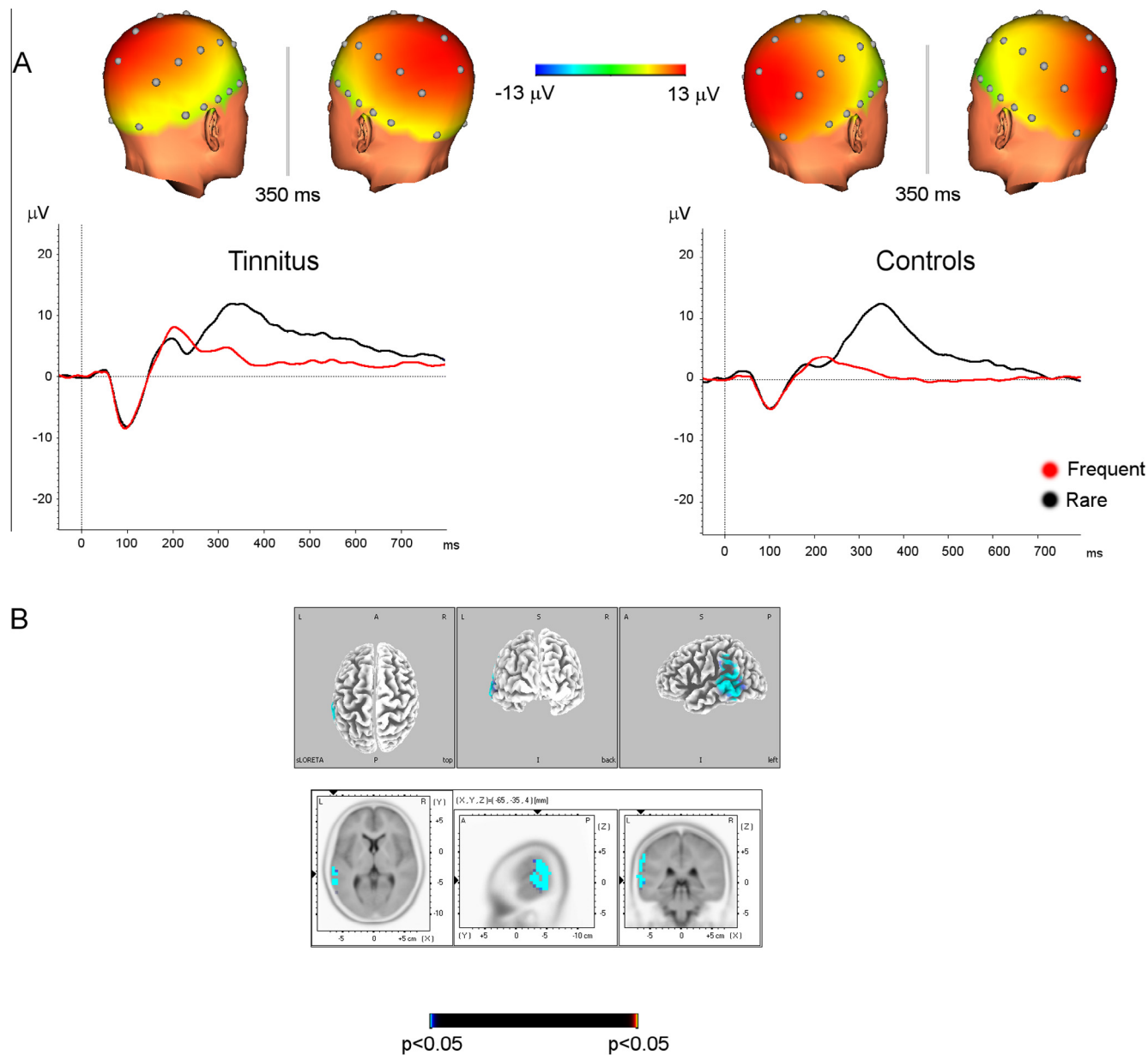


Fig. 4. P300 grand average in tinnitus sufferers and controls. (A) Scalp localization of P300 in subjects with tinnitus (left) and controls (right). Grand averages of the ERPs following frequent (red) and rare (black) stimulus over the Cz electrode are represented under the scalp maps. (B) Statistical maps of sLORETA solutions showing a significant lower activity in the left auditory cortex (BA22) in the tinnitus group. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Auditory (N100/P200) evoked potentials in tinnitus sufferers and controls, according to the rare and frequent stimulus conditions. Since data were not distributed normally, median and interquartile range (IQR) are exposed. Latency are expressed in ms and amplitude in μV .

		N100				P200			
		Freq		Rare		Freq		Rare	
		Latency	Amplitude	Latency	Amplitude	Latency	Amplitude	Latency	Amplitude
Patients	Median	104.00	-7.77	103.00	-8.28	210.00	6.23	185.00	6.43
	IQR	14.50	4.20	14.50	5.88	28.50	3.19	25.00	4.94
Controls	Median	110.00	-8.50	116.00	-11.80	202.00	9.43	196.00	8.36
	IQR	18.50	8.87	17.50	9.52	21.00	2.78	22.00	3.57

condition. Indeed, it is possible that alpha activity in the eyes closed condition might have masked the abnormally reduced beta sources activity also present in the closed eyes condition. Moreover, it is important to note that we did not find increased

delta, theta or gamma cortical sources – the role of the latter in perceptual processes being still under investigation (Sedley and Cunningham, 2013), as reported in other EEG studies (Ashton et al., 2007; Moazami-Goudarzi et al., 2010; Adjajian et al.,

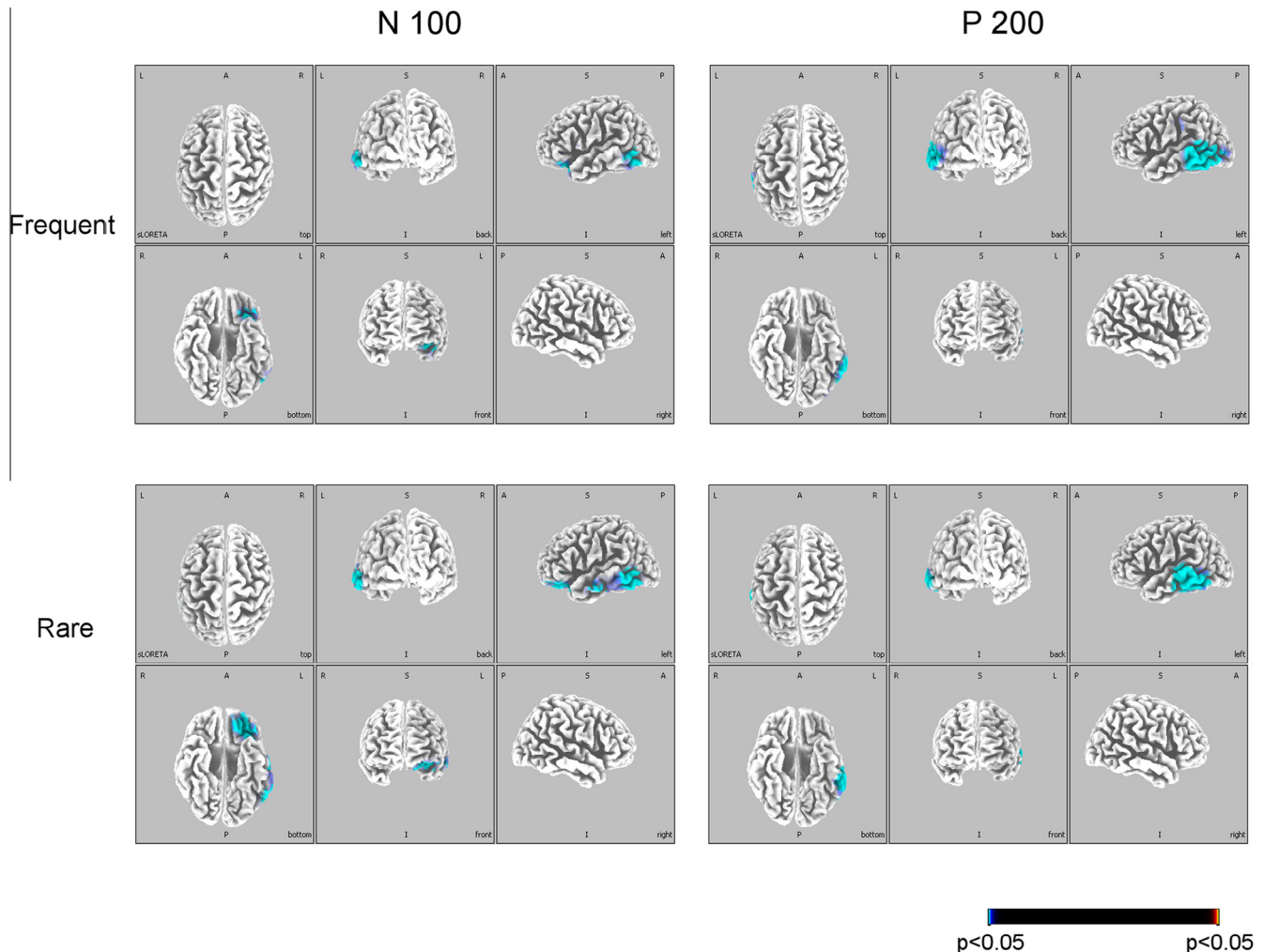


Fig. 5. Statistical differences of sLORETA solutions of the N100 and P200 sources between tinnitus sufferers and controls, demonstrating a significant lower cortical source in the left inferior temporal gyrus (auditory cortex, BA21) in the tinnitus group in both stimulus conditions (rare and frequent).

2012). This could be explained by the differences in clinical features of the tinnitus sufferers, among the studies. For example, age of onset may play a role in EEG findings and it should be considered that all of our subjects presented a long-lasting tinnitus (Song et al., 2015). One can also hypothesize that normoacoustic tinnitus sufferers would present with fewer lesions of the thalamic nuclei, which usually leads to low frequency bursts (Jeanmonod et al., 1996).

Our findings of hyperexcitability of cortico-thalamo-cortical circuits were further reinforced by the auditory evoked potentials data, showing shorter latencies of N100 in tinnitus sufferers, both for the “rare” and “frequent” stimulus conditions, and a shorter latency of the P200 only in the “rare” condition. Moreover, both N100 and P200 generators had lower CSD in the left inferior temporal gyrus. Like resting state EEG, ERPs’ data have been divergent in the literature, most probably due to the different stimulating protocols, subjects’ clinical features and number of inclusions. Smaller N100 peak amplitudes have been reported in tinnitus sufferers (Jacobson et al., 1996; Norena et al., 1999; Jacobson and McCaslin, 2003), most of them presenting with auditory deficits. Delb and colleagues (Delb et al., 2008) showed that N100 peak amplitude modulations could depend on the attention subjects pay to their tinnitus. In another EEG study, no differences in N100 peak amplitude were observed between tinnitus sufferers and controls (Lee et al., 2007). The mild impairment of the sensory

pathways, in our tinnitus sufferers’ group, might explain the absence of differences of peak amplitude between the two groups. However, the hyperexcitability of the thalamo-cortical circuits suggested by our resting-state results might explain the shorter latency observed in tinnitus sufferers.

The P300 is a cognitive ERP reflecting voluntary attention processing (Sutton et al., 1965; Polich and Kok, 1995) that has two subcomponents: the P3a (220–280 ms), larger over the frontocentral areas, occurring when the subject detects an unexpected stimulus in the absence of any prior instruction (Friedman et al., 1978); and the P3b (310–380 ms), centroparietal, that requires prior instruction of the participant (Courchesne et al., 1975; Squires et al., 1975). P3b would be related to an update in working memory processes following the presentation of new information (Donchin, 1981; Donchin and Coles, 1988). The amplitude of the P3b would be related to the attentional resource allocation with respect to top-down goals stored in short-term memory (Donchin and Coles, 1988; Polich and Heine, 1996). Thus, P3b amplitude increases when the stimulus is infrequent and relevant to the task (Squires et al., 1977; Castro and Díaz, 2001). On another hand, P3b latency would reflect the duration of the stimulus evaluation, independently of the time necessary to select and execute a response (Kutas et al., 1977; Johnson and Donchin, 1980; McCarthy and Donchin, 1981; Magliero et al., 1984). The fact that we did not find any significant differences between tinnitus sufferers and

controls in terms of P300 (P3b, in our case) peak amplitude, latency, or localization suggests that our tinnitus sufferers did not present alteration of active attention processes. Indeed, we only observed lower CSD of the P300 generators over the left auditory cortex. Since we obtained similar results with the N100 and P200 generators as well as in the resting state analysis, we believe that such decreased CSD of these evoked potentials generators might reflect the overall plastic changes in the auditory cortex observed in our group of tinnitus sufferers.

One limitation of our study resides in the low spatial resolution of our EEG montage and in the fact that electrode position was not digitized after each recording. The cortical source localizations evidenced in this study should thus be confirmed with a higher resolution EEG montage and using sensor digitalization.

In conclusion, our results are consistent with the hypothesis of a cortico-thalamo-cortical involvement in tinnitus, even in normoacoustic subjects. Our data suggest a hyperexcitability of the thalamo-cortical circuits involving the left inferior temporal and parietal lobules, as revealed by the resting-state and ERPs analyses. These results could be used to personalize treatment options in these subjects, especially using repetitive transcranial magnetic stimulation, which has shown benefits in tinnitus sufferers (Plewnia et al., 2003; De Ridder et al., 2006; Vanneste et al., 2011; Lehner et al., 2013). Indeed, the results we obtained in the opened eyes condition could be of particular interest to improve rTMS protocols in tinnitus. In concordance with De Ridder et al. (2005) who observed best rTMS results with a frequency of 20 Hz, our data suggest that using subjects' individual beta frequency to modulate cortical excitability could be of potential interest in tinnitus. And as Weisz et al. (2012) suggested, enlarging stimulation areas to non-auditory pathways (such as the parietal lobe) might improve tinnitus sufferers' condition.

Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

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