



Research paper

Neural substrates predicting improvement of tinnitus after cochlear implantation in patients with single-sided deafness



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ARTICLE INFO

Article history:

Received 22 November 2012

Received in revised form

15 January 2013

Accepted 2 February 2013

Available online 13 February 2013

ABSTRACT

Notwithstanding successful reduction of tinnitus after cochlear implantation (CI) in patients with single-sided deafness (SSD) in recent studies, neither the exact mechanism of suppression nor the predictors of the amount of improvement are fully understood yet. We collected quantitative electroencephalography (qEEG) data from nine SSD patients who underwent CI for tinnitus management. By correlating the degree of improvement in tinnitus intensity and tinnitus-related distress with preoperative source-localized qEEG findings and comparing qEEG findings of patients with marked improvement after CI with those with relatively slight improvement with regard to source-localized activity complimented by connectivity analysis, we attempted to find preoperative predictors of tinnitus improvement. Our results showed increased activities of the auditory cortex (AC), posterior cingulate cortex (PCC) and increased functional connectivity between the AC and PCC as negative prognostic factors for the reduction of tinnitus intensity after CI in patients with SSD. Also, relatively increased activity of the right dorsolateral prefrontal cortex and decreased connectivity between distress-related areas such as the orbitofrontal cortex/parahippocampus and sensory-perception areas such as the AC/precuneus were found in patients with relatively slight improvement in tinnitus-related distress as compared with those with marked improvement. The current study suggests that preoperative cortical oscillations can be applied to predict post-CI tinnitus reduction in patients with SSD.

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1. Introduction

Tinnitus, a perception of a noxious disabling internal sound without an external source, develops in 16–21% of adults at some point in their lifetime. Tinnitus interferes severely with the quality of life in 5–26% of the afflicted population (Heller, 2003; Krogh et al.,

2010). The development of tinnitus is frequently associated with auditory deafferentation due to sensorineural hearing loss (Eggermont and Roberts, 2004; Muhlneckel et al., 1998; Weisz et al., 2007b). This notion was supported by transient phantom sound perception after experimentally induced partial (Schaeffe et al., 2012) and complete (Del Bo et al., 2008) temporary auditory deprivation in normal subjects.

By stimulating a deafferented ascending auditory nervous system with a cochlear implant (CI), tinnitus could be suppressed significantly in 66–92% of the CI users with bilateral profound hearing loss (Amoodi et al., 2011; McKerrow et al., 1991; Ruckenstein et al., 2001). Several mechanisms of CI-mediated tinnitus suppression have been suggested. Acoustic masking provided by CI is claimed to be the primary mechanism of tinnitus suppression because the increased auditory information due to the CI may distract attention from the tinnitus (Andersson et al., 2009; Kleinjung et al., 2009). Also, plastic changes in the central auditory system and associated cortical areas by prolonged CI stimulation

Abbreviations: CI, cochlear implant; SSD, single-sided deafness; qEEG, quantitative electroencephalography; NRS, numeric rating scale; TQ, tinnitus questionnaire; MI, marked improvement; SI, slight improvement; sLORETA, standardized low-resolution brain electromagnetic tomography; MNI, Montreal Neurological Institute; PCC, posterior cingulate cortex; A2, secondary auditory cortex; A1, primary auditory cortex; DLPFC, dorsolateral prefrontal cortex; PHC, parahippocampus; OFC, orbitofrontal cortex; AC, auditory cortex; DMN, default mode network.

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(Giraud et al., 2001) and electrical stimulation resulting in contralateral residual inhibition and tinnitus suppression (Souliere et al., 1992) have been introduced as possible mechanisms.

As in patients with bilateral profound hearing loss and tinnitus, improvement of tinnitus by CI was also demonstrated in patients with single-sided deafness (SSD) and incapacitating tinnitus in the ipsilesional ear (Arndt et al., 2011; Buechner et al., 2010; Kleinjung et al., 2009; Punte et al., 2011; Ramos et al., 2012; Van de Heyning et al., 2008). However, neither the exact mechanism of suppression nor the predictors of the degree of improvement in tinnitus after CI for SSD are fully understood. Indeed, notwithstanding overall remarkable improvements in tinnitus intensity after CI in patients with SSD, not all participants benefited from the CI to the same degree and in the same situations (Arndt et al., 2011; Punte et al., 2011; Van de Heyning et al., 2008). In this regard, a decision to implant needs to be made on a case-by-case basis (Buechner et al., 2010).

From this viewpoint, it is essential to conduct a study to explore possible preoperative predictors of tinnitus improvement after CI in patients with SSD. By correlating the degree of tinnitus improvement with preoperative source-localized quantitative electroencephalography (qEEG) findings, we attempted to find the preoperative neural correlates of tinnitus improvement. Additionally, we compared qEEG findings of SSD patients with marked improvement after CI with those with relatively slight improvement by source-localization complimented by connectivity analysis.

2. Materials and methods

2.1. Participants

Nine patients with unilateral acquired profound sensorineural hearing loss and ipsilateral tinnitus underwent preoperative EEG and then CI with a Med-EL device (Combi 40+, Pulsar or Sonata Ti100™ device with a medium, FLEX SOFT, or FLEX EAS electrode) (Med-EL, Innsbruck, Austria). The selection criteria for CI were: 1) the duration of deafness less than 10 years; 2) tinnitus as a result of SSD; and 3) tinnitus loudness on a numeric rating scale (NRS) $\geq 6/10$ for at least 6 months and intractable by conventional therapies such as tinnitus retraining therapy. The exclusion criteria were: 1) depression defined as Beck Depression Index (Beck and Steer, 1984) ≥ 16 ; 2) the etiology of tinnitus deemed not to be due to SSD. The details of deafness and tinnitus side, tinnitus type, frequency (Hz) and loudness (dB SL) before implantation, pre- and 6 months post-fitting NRS scores for tinnitus loudness and subjective distress evaluated by tinnitus questionnaire (TQ) (Goebel and Hiller, 1994) scores for the nine CI subjects are summarized in Table 1. The 6 months post-fitting questionnaire was based on the patients' subjective ratings for the NRS loudness and TQ scores in their daily life (not specifically in noisy environments or in silence). By median split method (Schlee et al., 2012) as a data driven post-hoc stratification, we were able to test the group difference between a marked improvement (MI) group and a slight improvement (SI) group. All subjects in the MI group showed percent improvement of tinnitus intensity $\geq 66.7\%$ while all subjects in the SI group showed improvement $\leq 37.5\%$ (Table 1). By the median split, both the MI and SI groups showed no difference with regard to the side of deafness (two patients with right SSD and two with left SSD, each). In this way, the bias due to the difference in the deafness side could luckily be minimized. Meanwhile, the patients were also divided into the MI group and the SI group with regard to TQ improvement in the same way (Table 1). The percent improvements of tinnitus intensity and TQ did not reveal a statistically significant correlation (Spearman's $\rho = 0.48, P = 0.23$).

Table 1 Summary of tinnitus characteristics of the 9 cochlear implant subjects. Subjects are listed by the chronological order of operation.

Subject number	Etiology	Tinnitus side	Tinnitus character	Tinnitus Frequency (Hz)	Tinnitus duration (years)	Tinnitus loudness	NRS intensity, preop	NRS intensity, postop	Percent improvement, NRS intensity	Group assignment according to NRS intensity improvement	TQ preop	TQ postop	Percent improvement, TQ	Group assignment according to TQ improvement
1	SSNHL	Right	NBN	1500	13	20	8	6	25	SI	71	63	11.3	SI
2	MD	Left	NBN	4000	7	40	10	3	70	MI	78	41	47.4	MI
3	SSNHL	Left	PT	8000	9	25	8	3	62.5	MI	78	41	47.4	MI
4	MD	Right	PT	750	6	25	9	2	77.8	MI	57	47	17.5	SI
5	SSNHL	Right	PT	6000	0.9	40	9	3	66.7	MI	52	29	44.2	MI
6	SSNHL	Left	NBN	500	2	10	7	5	28.6	SI	60	44	26.7	SI
7	BM	Left	NBN	1000	2	5	7	1	85.7	MI	33	18	45.5	MI
8	SSNHL	Left	PT	8000	5	30	9	6	33.3	SI	62	56	9.7	SI
9	SSNHL	Right	PT	8000	5.5	20	8	5	37.5	SI	NA	NA	NA	NA

NRS, numeric rating scale; preop, preoperative; postop, postoperative; TQ, tinnitus questionnaire; SSNHL, sudden sensorineural hearing loss; MD, Meniere's disease; BM, bacterial meningitis; PT, pure tone; NBN, narrow band noise; SI, slight improvement group; MI, marked improvement group; NA, not available.

To explore general characteristics of the patients, EEGs of age- and sex-matched nine controls without any history of tinnitus were collected from our normative database and were compared with those of the patients.

2.2. EEG recording

EEGs were recorded for 5 min using the WinEEG software version 2.84.44 (Mitsar, St. Petersburg, Russia) in a fully lighted room shielded against sound and stray electric fields with eye-closed and sitting upright. The EEG was sampled with 19 electrodes in the standard 10–20 International placement referenced to linked ears while maintaining impedances below 5 k Ω at all electrodes. Data were recorded with a 1024 Hz sampling frequency, a 0.15 Hz high-pass filter and a 200 Hz low-pass filter. After recording, the data were processed off-line by resampling to 128 Hz and band-pass filtering (fast Fourier transform filter applying a Hanning window) with 2–44 Hz and then imported into the Eureka! software (Sherlin and Congedo, 2005). All episodic artifacts were removed from the EEG stream meticulously by manual inspection.

2.3. Source localization analysis

Standardized low-resolution brain electromagnetic tomography (sLORETA) (Pascual-Marqui, 2002), a functional imaging method based on certain electrophysiological and neuroanatomical constraints, was utilized to estimate the intracerebral sources generating the scalp-recorded electrical activity in each of the following eight frequency 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). In sLORETA, the cerebral cortex is modeled as a collection of 6239 voxels at 5 mm spatial resolution and is restricted to cortical gray matter and hippocampi in the digitized Montreal Neurological Institute (MNI) coordinates corrected to the Talairach coordinates, and neuronal activity is computed as current density ($\mu\text{A}/\text{mm}^2$) without assuming a predefined number of active sources (Fuchs et al., 2002).

Basically, sLORETA gives a single linear solution to the inverse problem of functional cortical localization based on extracranial measurements (Marco-Pallares et al., 2005) and generates images of standardized current density with no localization bias (Pascual-Marqui, 2002; Sekihara et al., 2005). The localization accuracy of sLORETA has repeatedly been validated by combining sLORETA with other localization methods such as structural magnetic resonance imaging (MRI) (Worrell et al., 2000), functional MRI (Mulert et al., 2004; Olbrich et al., 2009; Vitacco et al., 2002) and positron emission tomography (Dierks et al., 2000; Pizzagalli et al., 2004; Zumsteg et al., 2005). Especially, correct localization of deep brain structures such as the anterior cingulate cortex (Pizzagalli et al., 2001) and the mesial temporal lobe (Zumsteg et al., 2006) by sLORETA further validated localization accuracy.

2.4. Functional connectivity

Dynamic functional connectivity between 2 brain regions can be quantified as the “similarity,” such as linear dependence (coherence) and nonlinear dependence (phase synchronization), between time-varying signals recorded at the 2 regions (Worsley et al., 2005). However, any measure of dependence is highly contaminated with an instantaneous, non-physiological contribution due to volume conduction and low spatial resolution (Pascual-Marqui, 2007a). As a solution to this problem, a refined technique (i.e., Hermitian covariance matrices) that considerably removes confounding factors has been introduced (Pascual-Marqui, 2007b). Thus, this measure of dependence can be applied to any number of

brain areas whose activity can be estimated with sLORETA. In this method, measures of linear dependence between the multivariate time series are defined, and the measures are expressed as the sum of lagged and instantaneous dependence. Based on this principle, lagged connectivity among 28 ROIs based on previous tinnitus literature (Table 2) was calculated using the connectivity toolbox in sLORETA.

2.5. Statistical analysis

In order to identify preoperative neural correlates of tinnitus improvement, the log-current density was correlated with the percent improvement of NRS tinnitus intensity and TQ separately. Additionally, to identify potential differences between the MI and SI groups with regard to tinnitus intensity and TQ improvement, voxel-by-voxel analysis using sLORETA was performed for the 8 frequency band between-condition comparisons of the current density distribution. Both for correlation and group comparison analyses, statistical nonparametric mapping (SnPM) of sLORETA images were performed for each contrast using sLORETA's built-in voxelwise randomization tests (5000 permutations) and employing a log-*F*-ratio statistic for independent groups with a threshold $P < 0.05$. A correction for multiple comparisons in SnPM using random permutations (5000 permutations in the current study) has been validated and proven to give results, at least, similar to those obtained from a comparable statistical parametric mapping approach using a general linear model with multiple comparisons corrections derived from random field theory (Holmes et al., 1996; Nichols and Holmes, 2002).

For lagged connectivity differences, we compared differences between the MI and SI groups for each contrast employing the *t*-statistics for independent groups with a threshold $P < 0.05$, also corrected for multiple comparisons by conducting sLORETA-built-in voxelwise randomization tests (5000 permutations).

3. Results

3.1. Comparison between the patients and normal controls

Compared to the age- and sex-matched controls, the patients showed significantly increased activity in the right secondary

Table 2
Twenty-eight regions of interest and their references.

Regions of interest	References
Auditory cortices (BAs 41L, 41R, 42L, 42R, 21L, 22R, 22L, and 22R)	(Muhlnickel et al., 1998; Smits et al., 2007; Weisz et al., 2007c)
Parahippocampus (BAs 27L, 27R, 29L, and 29R)	(Landgrebe et al., 2009)
Dorsal anterior cingulate cortex (BAs 24L and 24R)	(De Ridder et al., 2011a; Schlee et al., 2009)
Pregenuar anterior cingulate cortex (BAs 32L and 32R)	(De Ridder et al., 2011a)
Subgenual anterior cingulate cortex (BAs 25L and 25R)	(Vanneste et al., 2010)
Posterior cingulate cortex (BAs 31L and 31R)	(De Ridder et al., 2011a)
Precuneus (BAs 7L and 7R)	(Schecklmann et al., 2013; Vanneste et al., 2010) as well as source localization analysis results of the current study
Orbitofrontal cortex (BAs 11L, 11R, 10L, and 10R)	(Vanneste et al., 2010) as well as source localization analysis results of the current study
Insula (BAs 13L and 13R)	(De Ridder et al., 2011a; van der Loo et al., 2011)

BA, Brodmann area; L, left; R, right.

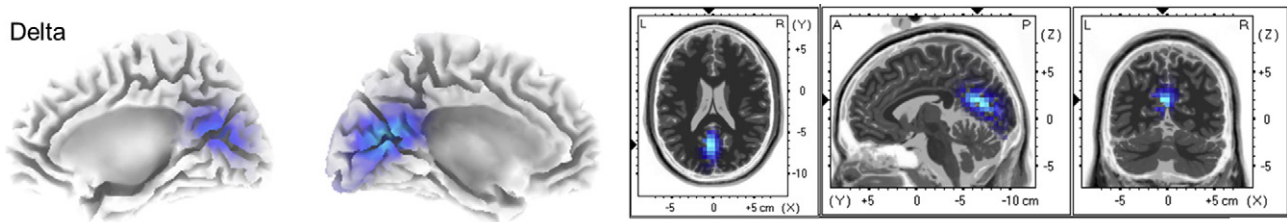


Fig. 1. Standardized low-resolution brain electromagnetic tomography (sLORETA) correlation analysis with the percent improvement of NRS tinnitus intensity. The activity of the posterior cingulate cortex for the delta band was negatively correlated with the percent improvement of NRS intensity on a trend level ($P = 0.07$).

auditory cortex (A2, BA 21) and the right inferior frontal gyrus (BA 47) for the delta band. For the other seven frequency bands no significant differences were found between the patients and controls.

3.2. Improvement in NRS tinnitus intensity

3.2.1. Correlation analysis

No cortical regions displayed a significant correlation with the percent improvement of NRS tinnitus intensity. However, the activity of the posterior cingulate cortex (PCC) for the delta band was negatively correlated with the percent improvement of NRS intensity on a trend level ($P = 0.07$) (Fig. 1). No significant correlations were found between functional connectivity and the improvement in NRS tinnitus intensity.

3.2.2. Group comparison: source localization analysis

Compared to the MI group, the SI group demonstrated significantly increased activities in the left A2 (BA 21) for the delta and gamma frequency bands and in the left temporal pole (BA 38) for the beta1 frequency band ($P < 0.05$) (Fig. 2). Meanwhile, the contrast “MI group–SI group” displayed no significantly increased or decreased activities.

3.2.3. Group comparison: functional connectivity

The SI group revealed increased functional connectivity between the left primary auditory cortex (A1, BA 41) and the right PCC for the delta frequency band as compared with the MI group ($P < 0.05$, Fig. 3). For the other seven frequency bands no significant differences were found between the two groups. Also, the contrast “MI group–SI group” displayed no significantly increased or decreased connectivity throughout the eight frequency bands.

3.3. Improvement in TQ score

3.3.1. Correlation analysis

The activity of the right dorsolateral prefrontal cortex (DLPFC, BA 9) for the alpha2 frequency band showed significantly negative correlation with the percent improvement of TQ score ($P < 0.05$) (Fig. 4). No significant correlations were found between functional connectivity and the improvement in TQ score.

3.3.2. Group comparison: source localization analysis

No statistically significant differences were found between the MI and SI groups, but the SI group demonstrated increased activities on a trend level ($P = 0.09$) in the right DLPFC (BA 10) for the beta3 and gamma frequency bands as compared with the MI group

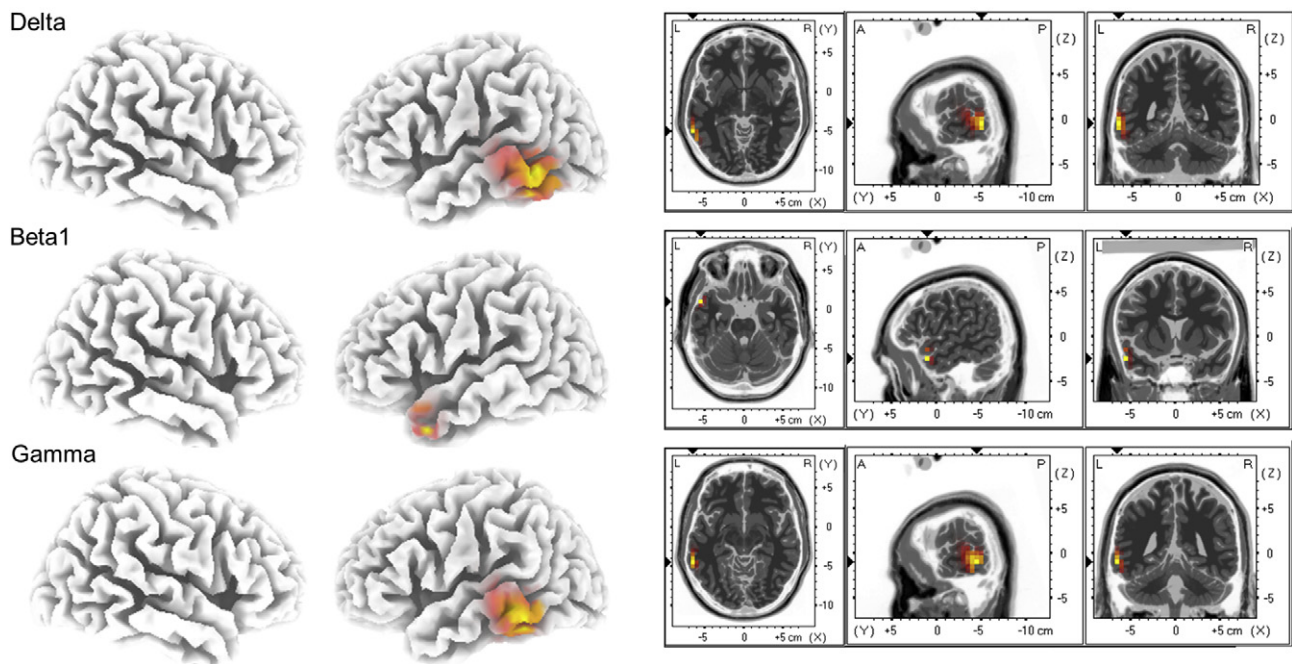


Fig. 2. Standardized low-resolution brain electromagnetic tomography (sLORETA) contrast analysis between the marked improvement (MI) and slight improvement (SI) groups with regard to NRS tinnitus intensity. Compared to the MI group, the SI group demonstrated significantly increased activities in the left secondary auditory cortex for the delta and gamma frequency bands and in the left temporal pole for the beta1 frequency band ($P < 0.05$).

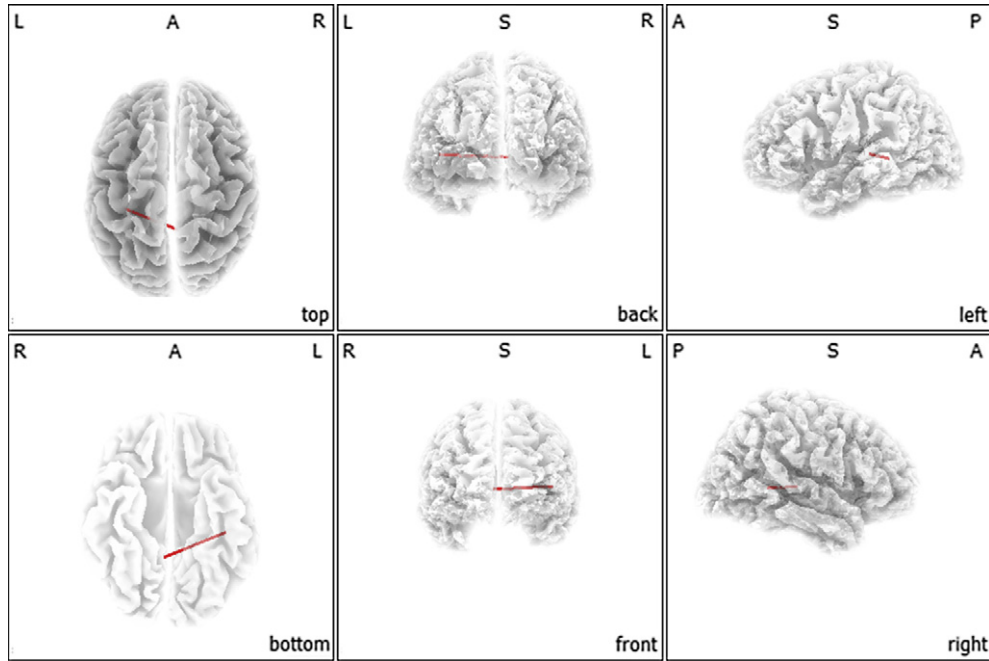


Fig. 3. Connectivity contrast analysis the marked improvement (MI) and slight improvement (SI) groups with regard to NRS tinnitus intensity. The SI group showed increased functional connectivity between the left primary auditory cortex and the right PCC for the delta frequency band as compared with the MI group ($P < 0.05$).

(Fig. 5). Meanwhile, the contrast “MI group–SI group” displayed no significantly increased or decreased activities.

3.3.3. Group comparison: functional connectivity

The SI group revealed significantly decreased functional connectivity between bilateral A1s (BA 41), between the right A1 and the left parahippocampus (PHC), between the left A1 and the right PCC and between the right orbitofrontal cortex (OFC) and the left precuneus for the gamma frequency band as compared with the MI group ($P < 0.05$, Fig. 6). For the other seven frequency bands no significant differences were found between the two groups. Meanwhile, the contrast “MI group–SI group” displayed no significantly increased or decreased connectivity throughout the eight frequency bands.

4. Discussion

In the current study, we investigated the neural correlates functioning as biomarkers of tinnitus improvement after CI in patients with SSD. Patients with relatively slight improvement in the NRS intensity demonstrated significantly increased activities in the left A2 for the delta and gamma frequency bands and in the left temporal pole for the beta1 frequency band as well as increased functional connectivity between the left A1 and the right PCC for the delta frequency band as compared with those with marked

improvement. Additionally, the activity of the PCC for the delta band showed negative correlation on a trend level ($P = 0.07$) with the percent improvement of NRS intensity. Meanwhile, the right DLPFC activity showed significantly negative correlation with the percent improvement of TQ score for the alpha2 band, and also showed a trend-level activity increase in the SI group relative to that in the MI group for the beta3 and gamma frequency bands. The results are summarized in Table 3.

4.1. Tinnitus perception: beyond sensory neocortex to the default mode network

Tinnitus has been found to be associated with increased activation of the auditory cortex (AC) secondary to excitatory/inhibitory imbalance or an adjustment of auditory gain mechanisms (Norena, 2011). Conscious perception of auditory signals correlates with gamma band activity in the AC (Joliot et al., 1994). Also in patients with unilateral tinnitus, several EEG or magnetoencephalography studies have revealed reduced alpha while increased delta and gamma activity in the contralateral AC (Weisz et al., 2007a, 2005). Additionally, a recent meta-analysis on PET studies in uni- or bilateral tinnitus patients has shown increased regional cerebral blood flow in the left A1 and bilateral A2 (Song et al., 2012). Moreover, perceived tinnitus intensity is correlated with increased contralateral gamma band activity in the AC (van der Loo et al.,

Alpha2

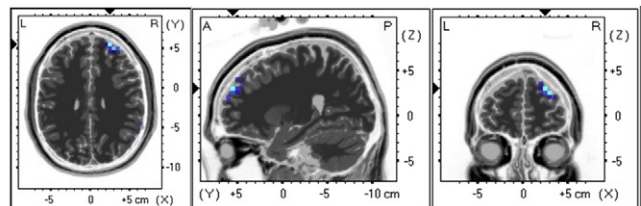
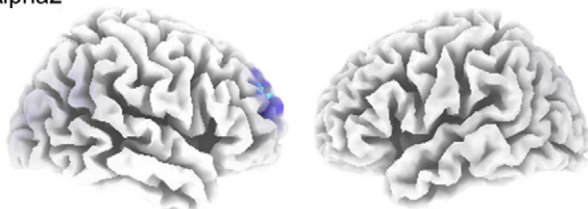


Fig. 4. Standardized low-resolution brain electromagnetic tomography (sLORETA) correlation analysis with the percent improvement of TQ score. The activity of the right dorsolateral prefrontal cortex for the alpha2 frequency band showed significantly negative correlation with the percent improvement of TQ score ($P < 0.05$).

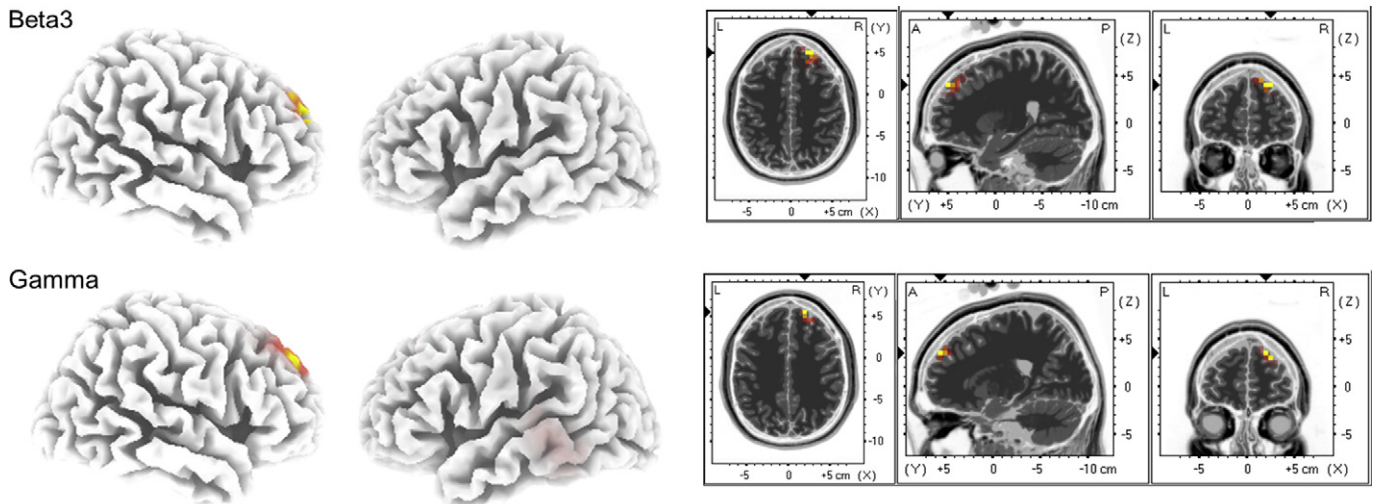


Fig. 5. Standardized low-resolution brain electromagnetic tomography (sLORETA) contrast analysis between the marked improvement (MI) and slight improvement (SI) groups with regard to TQ score. The SI group demonstrated increased activities on a trend level ($P = 0.09$) in the right dorsolateral prefrontal cortex for the beta3 and gamma frequency bands as compared with the MI group.

2009). The increased activity of the AC may explain why tinnitus is suppressed by transcranial magnetic stimulation to the AC (De Ridder et al., 2005; Plewnia et al., 2003). The current study showing significantly increased activities in A2 for the delta and gamma frequency bands in patients with less NRS intensity improvement as compared to those with much improvement suggests that higher preoperative activity in A2 may be an unfavorable prognostic indicator after CI in patients with SSD.

We also found near-significant negative correlation ($p = 0.07$) between the PCC activity for the delta band and NRS intensity improvement and increased functional connectivity between the left A1 and the right PCC for the delta band in the SI group as

compared with the MI group. Activation in the PCC has been associated with the brain's default mode network (DMN) (Raichle and Snyder, 2007, 2001), a specific set of brain regions activated when people are occupied with internally focused tasks (Schlee et al., 2012). The PCC plays a crucial role in auditory perception, as shown in persistent vegetative state patients in whom activation induced by auditory stimulation is restricted to the bilateral A1, without functional connectivity to the areas encompassing the DMN including the PCC (Boly et al., 2004; Laureys et al., 2000). Recent findings in tinnitus research suggest that tinnitus generators may become integrated in the DMN in tinnitus patients (De Ridder et al., 2011b; Vanneste and De Ridder, 2012). In this

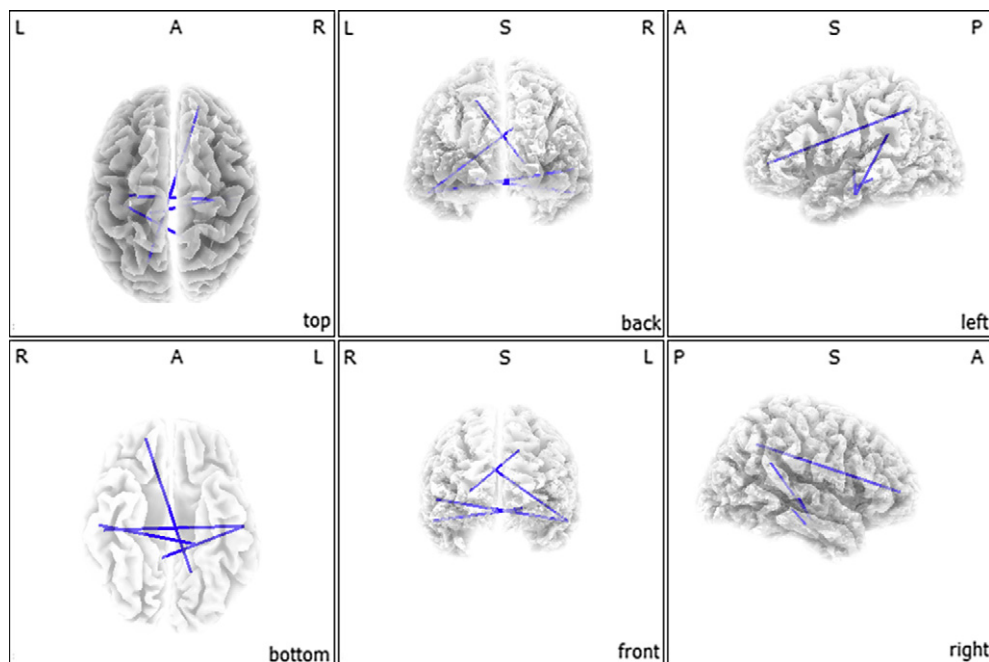


Fig. 6. Connectivity contrast analysis the marked improvement (MI) and slight improvement (SI) groups with regard to TQ score. The SI group revealed significantly decreased functional connectivity between the bilateral primary auditory cortices (A1s), between the right A1 and the left parahippocampus, between the left A1 and the right posterior cingulate cortex and between the right orbitofrontal cortex and the left precuneus for the gamma frequency band as compared with the MI group ($P < 0.05$).

Table 3

Summary of the brain areas found to be predictive of slight improvement of tinnitus with regard to the numeric rating scale intensity and the tinnitus questionnaire score.

Parameters	Brain areas	Significant differences compared to the marked improvement group
NRS intensity	Left A2	Increased activities for the delta and gamma frequency bands
	Left temporal pole	Increased activity for the beta 1 frequency band
	Left A1–right PCC	Increased functional connectivity for the delta frequency band
TQ score	Right DLPFC	Negative correlation with the percent improvement of TQ score for the alpha2 band
	Left A1–right A1, right A1–left PHC, left A1–right PCC, right OFC–left precuneus	Decreased functional connectivity for the gamma frequency band

NRS, numeric rating scale; TQ, tinnitus questionnaire; A2, secondary auditory cortex; PCC, posterior cingulate cortex; A1, primary auditory cortex; PHC, parahippocampus; OFC, orbitofrontal cortex.

regard, the increased connectivity between the A1 and PCC in the SI group as well as negative correlation between the PCC activity and NRS intensity improvement may indicate an ominous involvement of the DMN in patients who showed relatively minute improvement in NRS tinnitus intensity. In other words, tinnitus may already have become a norm by spreading beyond the sensory neocortex and being connected to the DMN and thus NRS intensity was relatively irreversible in these relatively resistant patients.

4.2. Top–down modulation toward distress by the DLPFC

After being perceived, tinnitus is connected to an emotional response inducing distress. The DLPFC has been suggested as one of the responsible regions for this connection between perception and emotion. The DLPFC has both facilitatory effect on auditory sensory memory storage (Alain et al., 1998) and inhibitory effect on the inputs to the A1 (Knight et al., 1989). Also, the DLPFC is associated with auditory attention (Alain et al., 1998; Voisin et al., 2006) resulting in top–down modulation of auditory processing (Mitchell et al., 2005) and this notion was also applied to explain pathogenesis of tinnitus as the result of a dysfunction in the top–down inhibitory processes (Norena et al., 1999). Especially, the DLPFC is suggested to be an area involved in the integration of emotion and cognition (Ursu et al., 2011) by providing top–down “guided activation” that biases representations toward context-appropriate responding (Davidson, 2003). Also in tinnitus, the prefrontal cortex has been proposed as a “candidate for the integration of sensory and emotional aspects of tinnitus” (Jastreboff, 1990). This notion has further been confirmed by revealing the association between the activity of the DLPFC and tinnitus-related distress (Vanneste et al., 2010) and showing improvement of tinnitus distress by repetitive transcranial magnetic stimulation (Kreuzer et al., 2011) and transcranial direct current stimulation (Faber et al., 2012) targeting the DLPFC.

In the current study, the activity of the DLPFC was found to be another important preoperative biomarker with regard to the improvement of tinnitus-related distress after CI in patients with SSD. Viewing from the above-mentioned roles of the DLPFC in tinnitus, the negative correlation of the right DLPFC with the improvement of TQ may designate a tighter connection between tinnitus perception and affective component by a top–down affective modulation by the right DLPFC may have been an obstacle to suppress tinnitus-related distress by CI.

4.3. Connectivity between perceptual and distress networks

Significantly decreased functional connectivity between right A1 and left PHC and between right OFC and left precuneus for the gamma frequency band was found in patients with slight TQ improvement as compared with those with marked improvement. The PHC and the right OFC has been suggested to be components of tinnitus-related distress circuits (Joos et al., 2012). Meanwhile, the precuneus is a component of DMN and may contribute to tinnitus perception (De Ridder et al., 2011b). From these observations, weaker connectivity between distress-related areas and auditory/perception areas may have resulted in less effective suppression of distress by the electrical stimulation.

Changes in loudness and distress are two main parameters when evaluating the efficacy of tinnitus treatment (Langguth et al., 2007). Because these two parameters were not significantly correlated in the current series of CI subjects, and it has been shown that these clinical characteristics correlate with different brain networks (De Ridder et al., 2011a; De Ridder et al., 2011b; Joos et al., 2012; Vanneste et al., 2010) the preoperative biomarkers for the improvement of tinnitus loudness and related distress should be explored separately. As described above, a network mainly based on the AC and the PCC may be responsible for the improvement of NRS tinnitus intensity, while another network mainly composed of prefrontal regions such as the DLPFC, the OFC and the PHC may be responsible for the improvement of tinnitus-related distress. The fact that these two networks are non-overlapping suggests that CI-mediated improvements in tinnitus loudness and distress have different mechanisms.

4.4. Limitations of the current study and proposed future studies

To our knowledge, this is the first study addressing possible preoperative biomarkers of tinnitus improvement after CI in patients with SSD. Although we found several important factors that may be correlated with the degree of improvement, there are several limitations that should be verified in future studies. First, as previously mentioned, only a small group with SSD and tinnitus in our series underwent preoperative qEEG. This may have resulted in limited statistical power, as seen in the correlation analysis showing only near-significant correlation ($P = 0.07$) between the PCC activity for the delta band and NRS intensity improvement. Although the connectivity analysis revealed increased connectivity to the PCC in the SI group, the limited statistical power warrants future study with larger number of participants to further evaluate this trend-level correlation. Although four most resistant cases to CI with regard to NRS intensity improvement were included, and these four patients are representative of slight improvement after CI because only these four showed an improvement less than 40% (the other 26 patients in our series showed an improvement of more than 60%), future study with larger number of subjects is needed to confirm the current findings. Additionally, due to the limited number of study subjects, we could not match the mode of deafness, i.e. sudden or progressive hearing loss, between the two groups. Because subjects with sudden hearing loss might be different from those with progressive hearing loss in the plastic changes of their brains, a future study with a larger number of subjects matched for the etiology of hearing loss should be performed. Furthermore, postoperative qEEG findings as well as changes in between pre- and postoperative qEEGs should also be compared between marked and slight improvement groups to better understand cortical changes that are critical for the improvement of tinnitus after CI in patients with SSD. According to the patients' report, the tinnitus loudness after CI did not show huge difference between in a noisy environment and in silence, but

this was neither assessed using an NRS scale nor evaluated in a sound-proof environment such as in an audiometry booth. Since the differences with regard to patients' subjective responses to the questionnaire and qEEG findings between in a noisy environment and in absolute silence may be crucial for understanding the mechanism that underlies the improvement of tinnitus following CI, future studies addressing these issues should be performed.

5. Conclusions

Taken together, our preliminary data showed increased activity of the AC, PCC and increased functional connectivity between the AC and the PCC as the negative preoperative prognostic factors for the reduction of tinnitus intensity after CI in patients with SSD. Also, increased activity of the right DLPFC and decreased connectivity between distress-related areas and auditory/perception areas may be ominous preoperative biomarkers for the improvement of tinnitus-related distress. With future studies including post-operative qEEG findings in a larger group, our preliminary findings may help in developing tailor-made counseling and patient selection for CI in patients with SSD.

Funding

This work was supported by Research Foundation Flanders (FWO), Tinnitus Research Initiative, TOP project University Antwerp, The Neurological Foundation of New Zealand and the Korean Science and Engineering Foundation (KOSEF) grant funded by the Korean government (MOST) (no. 2012-0030102).

Acknowledgments

The authors thank Jan Ost, Bram Van Achteren, Bjorn Devree and Pieter van Looy for their help in preparing this manuscript.

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