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"Distressed aging": the differences in brain activity between early- and late-onset tinnitus

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ABSTRACT

Recent findings regarding different characteristics according to the age of tinnitus onset prompted us to conduct a study on the differences in tinnitus-related neural correlates between late-onset tinnitus (LOT; mean onset age, 60.4 years) and early-onset tinnitus (EOT; mean onset age, 29.7 years) groups. Hence, we collected quantitative electroencephalography findings of 29 participants with LOT and 30 with EOT, and from 59 controls. We then compared the results between the 2 groups and between the tinnitus groups and age- and sex-matched control groups using resting state electroencephalography source-localized activity and connectivity analyses. Compared with the EOT and older control groups, the LOT group demonstrated increased localized activity and functional connectivity in components of previously described tinnitus distress networks, and the default mode and intrinsic alertness networks, such as the prefrontal cortices, dorsal anterior cingulate cortex, and insula. The current findings of intrinsic differences in tinnitus-related neural activity between the LOT and EOT groups might be applicable for planning individualized treatment modalities according to age of onset. Moreover, differences with regard to the age of tinnitus onset might be a milestone for future studies on onset-related differences in other similar pathologies, such as pain or depression.

1. Introduction

Tinnitus is an auditory phantom phenomenon of a sound perception in the absence of any objective physical sound source (Jastreboff, 1990). Tinnitus afflicts 5%–15% of the western population, and tinnitus severely affects the quality of life for 2–3 in 100 individuals, because it causes a considerable amount of distress (Heller, 2003). The neurobiological basis of tinnitus is characterized by an ongoing abnormal spontaneous activity and reorganization of the auditory central nervous system (Moazami-Goudarzi et al., 2010; Weisz et al., 2005b). However, nonauditory brain structures, such as the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), amygdala, and the parahippocampus, have been suggested to be associated with the perception of tinnitus and its salience, tinnitus-related distress, and tinnitus memory (De Ridder et al., 2011a).

Tinnitus is more problematic for the geriatric population, because more than 30% of adults aged 55–99 years report having experienced tinnitus (Sindhusake et al., 2003). Further, the prevalence of chronic tinnitus increases with age, peaking at 60–69 years of age (Shargorodsky et al., 2010). This high prevalence of tinnitus in the geriatric population can been partly explained by the fact that hearing loss is an important risk factor for tinnitus, and that the prevalence of hearing loss increases with age (Spoor, 1967). Additionally, recent studies have discovered that late-onset tinnitus (LOT) differs from early-onset tinnitus (EOT) not only with regard to prevalence, but also with regard to tinnitus-related distress. That is, participants with LOT are more abruptly distressed and suffer significantly more than those with EOT (Schlee et al., 2011).

These differences in tinnitus-related distress according to age at onset might be related to differences in neural correlates associated with tinnitus between LOT and EOT individuals. Considering that aging is associated with functional disruption or underrecruitment of cortical networks (Logan et al., 2002) and compensatory cortical recruitment (Davis et al., 2008), and that neuroplastic processes play a crucial role in the generation of tinnitus and its related distress, we hypothesized that neural correlates involved in the

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generation of tinnitus and related distress might be different between LOT and EOT groups. These potential differences might lead to different treatment options for patients with EOT and LOT.

Hence, it is essential to perform a study that examines the differences in neural correlates associated with tinnitus between LOT and EOT groups. By matching all known affecting factors for tinnitus, excluding age of onset, we would obtain onset-related differences in the neural correlates for tinnitus-related distress. Moreover, by comparing differences in these results between young and old control groups, we explored whether these results merely originated from the normal aging process. We further attempted to unravel the distinct nature of the tinnitus brain, the possibility of individualized treatment modalities according to the age of onset, and a possible universal mechanism that might be found in other pathologies.

Hereinafter, we describe our results, which were analyzed by source-localized quantitative electroencephalography, and discuss possible explanations for the differences.

2. Methods

2.1. Participants

To recruit a homogenous study group with regard to tinnitus characteristics, we selected participants with narrow-band noise (NBN) bilateral tinnitus from the database of the multidisciplinary Tinnitus Research Initiative Clinic at the University Hospital of Antwerp, Belgium. Individuals with pulsatile tinnitus, Ménière's disease, otosclerosis, chronic headache, hearing loss exceeding the range of serviceable hearing (40 dB) (Farrior, 1956) in at least 1 ear, neurological disorders such as brain tumors, and individuals being treated for mental disorders were not included in the study to obtain a homogeneous sample. As a result, 59 participants with NBN bilateral tinnitus ($n = 59$; 40 male and 19 female) with a mean age of 48.5 years (range, 20–79 years) were included.

Similar to the tinnitus participants, 59 individuals who did not have tinnitus were selected as a control group from a normative database consisting of 235 participants who underwent an electroencephalogram (EEG) analysis. Using 1-by-1 matching to the tinnitus participants, a control group consisting of 41 male and 18 female participants with a mean age of 47.1 years (range, 18–81 years) was selected. Recordings were made under similar circumstances (i.e., in a fully lighted room with participants sitting upright in a comfortable chair with their eyes closed). None of these participants suffered from tinnitus or hearing loss. Exclusion criteria for the control participants were known Ménière's disease, chronic headache, neurological disorders such as brain tumors, and individuals being treated for psychiatric or neurological illness, drug and/or alcohol abuse, current psychotropic and/or central nervous system active medications, or history of head injury (with loss of consciousness) or seizures.

2.2. Subgrouping

Of the 59 participants, 29 with a mean age of onset of 60.4 ± 6.9 years were allocated to the LOT group and 30 with a mean age of onset of 29.7 ± 8.7 years were allocated to the EOT group. No significant differences were found between the EOT and LOT groups for sex, tinnitus duration, Numeric Rating Scale intensity, Numeric Rating Scale distress, total Tinnitus Questionnaire scores (Goebel and Hiller, 1994), or hearing threshold at the tinnitus frequency (all p values >0.3) (Table 1). Therefore, the EOT and LOT groups were maximally matched for all possible influencing factors except age of onset. All patients underwent pure tone audiometry to evaluate hearing threshold. Tinnitus matching was performed by assessing tinnitus pitch (frequency) and tinnitus intensity. No significant differences were found for hearing loss between the 2 groups, as measured by the loss in decibels at the tinnitus frequency (Table 1).

Table 1
Characteristics of participants with tinnitus

	Late-onset tinnitus group ($n = 29$)	Early-onset tinnitus group ($n = 30$)	P
Age (y)	64.5 ± 6.8	33.1 ± 9.2	<0.001
Age of onset (y)	60.4 ± 6.9	29.7 ± 8.7	<0.001
Male:female	20:9	20:10	—
Tinnitus duration (y)	4.0 ± 3.1	3.4 ± 4.2	0.524
Total score on Tinnitus Questionnaire	43.8 ± 17.1	40.3 ± 19.2	0.467
Hearing threshold at tinnitus frequency (dB HL)	31.7 ± 15.7	27.5 ± 17.9	0.355
NRS intensity	6.34 ± 1.95	5.45 ± 2.54	0.145
NRS distress	6.27 ± 1.95	5.60 ± 3.04	0.327

Key: dB HL, hearing loss in decibels; NRS, numeric rating scale.

The control group was subdivided into an old control group and a young control group to compare the LOT and EOT groups. No significant differences were found for sex ($p = 0.54$) or age ($p = 0.66$) between the LOT group and the old control group, and between the EOT and the young control group.

2.3. EEG recording

Participants were requested to refrain from alcohol consumption for 24 hours before EEG recording and from caffeinated beverages on the day of recording to avoid alcohol-related changes in the EEG (Vanneste and De Ridder, 2012) or a caffeine-induced alpha decrease in the EEG (Barry et al., 2011; Foxe et al., 2012).

EEG recordings were obtained in a fully lighted room shielded against sound and stray electric fields with each participant sitting upright in a comfortable chair. The actual recording lasted approximately 5 minutes. The EEG was sampled with 19 electrodes in the standard 10–20 International placement referenced to linked ears, and impedances remained at <5 kΩ. Data were collected in an eyes-closed condition (sampling rate = 1024 Hz, band-passed 0.15–200 Hz) using WinEEG software version 2.84.44 (Mitsar, St. Petersburg, Russia; available at: http://www.mitsar-medical.com). Data were resampled to 128 Hz, band-pass filtered (fast Fourier transform filter) to 2–44 Hz, subsequently transposed into Eureka! Software (Sherlin and Congedo, 2005; available at http://www.novatecheeg.com), plotted, and carefully inspected for manual artifact rejection. All episodic artifacts, including eye blinks, eye movements, teeth clenching, body movement, or electrocardiography artifacts were removed from the EEG stream. Additionally, an independent component analysis (ICA) was conducted to further verify if all artifacts were excluded. We compared the power spectra using 2 approaches to investigate the effect of possible ICA component rejection: (1) after visual artifact rejection only and (2) after an additional ICA component rejection. The mean power in delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz), and gamma (30.5–45 Hz) frequency bands did not show a significant difference between the 2 approaches. Therefore, we reported the results of ICA-corrected data. Average Fourier cross-spectral matrices were computed for the aforementioned bands from delta to gamma.

2.4. Source localization analysis

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 8 frequency bands (Pascual-Marqui, 2002). sLORETA computes electric neuronal activity as current density (A/m^2) without assuming a predefined number of active sources. The sLORETA solution space consists of 6239 voxels (voxel size: $5 \times 5 \times 5$ mm) and is restricted to cortical gray matter and hippocampi, as defined by the 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). sLORETA tomography has received considerable validation from studies combining low-resolution brain electromagnetic tomography with other established localization methods such as structural magnetic resonance imaging (Worrell et al., 2000), functional magnetic resonance imaging (Mulert et al., 2004; Vitacco et al., 2002), and positron emission tomography (Dierks et al., 2000; Pizzagalli et al., 2004; Zumsteg et al., 2005). Further sLORETA validation has been based on accepting as reasonable evidence the localization findings obtained from previously performed studies using invasive, implanted depth electrodes for clinical cases of epilepsy (Zumsteg et al., 2006a, 2006c) and cognitive event-related potentials (Volpe et al., 2007). It is noteworthy that deep brain structures such as the ACC (Pizzagalli et al., 2001) and the mesial temporal lobe (Zumsteg et al., 2006b) have been correctly localized with this method.

2.5. Region of interest (ROI) analysis

The sLORETA contrast between the LOT group and the old control group yielded decreased activity in the left primary auditory cortex (A1) for the alpha frequency band. Previous researchers have indicated that individuals with tinnitus are characterized by a marked reduction in alpha power together with an enhancement in delta as compared with normal control subjects (Weisz et al., 2005a). To compare our results with previous reports, the log-transformed electric current density was averaged across all voxels belonging to the ROIs composed of left A1s (Brodmann areas [BAs] 41 and 42) separately for the delta frequency band. Independent *t* tests were performed to compare the mean current density values of the LOT group and the old control group.

2.6. Functional connectivity analysis

Dynamic functional connectivity between 2 brain regions has been 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, nonphysiological contribution caused by volume conduction and low spatial resolution (Pascual-Marqui, 2007a). As a solution to this problem, Pascual-Marqui introduced a refined technique (i.e., Hermitian covariance matrices) that considerably removes this confounding factor (Pascual-Marqui, 2007b). Thus, 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. In this method, measures of linear dependence (coherence) between the multivariate time series are defined, and the measures are expressed as the sum of lagged and instantaneous dependence. The measures are nonnegative and take the value 0 only when there is independence of the pertinent type and they are defined in the frequency domains from delta to gamma bands as described in section 2.3. Based on this principle, lagged connectivity was calculated using the connectivity toolbox in sLORETA. Twenty-eight ROIs were defined based on previous tinnitus literature (Table 2), and the findings of the current study were based on the source localization analysis results (e.g., the precuneus and posterior cingulate cortex; PCC).

Table 2
Twenty-eight regions of interest and their references

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

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

A recent study indicated that the medial temporal lobe and posterior cingulum demonstrate the most significant normal aging-related changes in neural functional connectivity (Schlee et al., 2012). To compare our data quantitatively with the results of Schlee et al., we further calculated average weighted lagged linear connectivity of the medial temporal lobe and PCC in the LOT, EOT, old control, and young control groups and compared the differences among these 4 groups. To measure the average weighted connectivity, all 84 ROIs available in sLORETA were selected, and the lagged linear connectivity between the medial temporal lobe and the other 83 ROIs and between the posterior cingulum and the other 83 ROIs were calculated using the connectivity toolbox of sLORETA for each participant and averaged for each group. All 83 weighted measures of connectivity linking to the medial temporal lobe (and the posterior cingulum respectively) were averaged throughout the 8 frequency bands to calculate the average connectivity of the medial lobe and the posterior cingulum and compared between the groups.

2.7. Statistical analysis

sLORETA was used to perform a voxel-by-voxel analysis (comprising 6239 voxels each) for the 8 different frequency bands in the between-condition comparisons of the current density distribution to identify potential differences in brain electrical activity between the groups. Nonparametric statistical analyses of functional sLORETA images (statistical nonparametric mapping) were performed for each contrast using the sLORETA built-in voxelwise randomization tests (5000 permutations) and employing the *t* statistic for independent groups with a corrected threshold of $p < 0.05$. As explained by Nichols and Holmes, the statistical nonparametric mapping method does not rely on an assumption of a Gaussian distribution for the validity and corrects for all multiple comparisons (i.e., for the collection of tests performed for all voxels and for all frequency bands) by employing a locally pooled (smoothed) variance estimate that outperforms the comparable statistical parametric mapping approach (Nichols and Holmes, 2002). In this way, differences between the LOT and EOT groups, LOT and old control groups, EOT and young control groups, and the old and young control groups were assessed.

For lagged connectivity differences, we compared differences between the LOT and EOT groups and between the old and young control groups for each contrast using the *t* statistic for independent groups with a corrected threshold of $p < 0.05$. The significance threshold was based on a permutation test with 5000 permutations. An analysis of variance (ANOVA) was performed separately for the medial temporal lobe and for the posterior cingulum as a dependent variable with age (late-onset vs. early-onset) and group (tinnitus vs. control) as independent variables for the weighted connectivity comparison.

3. Results

3.1. Source localization analysis

3.1.1. The LOT group versus the EOT group

Compared with the EOT group, the LOT group showed significantly increased activities in the DLPFC (BA 9), the left side for beta3, and bilaterally for the gamma frequency bands in the right orbitofrontal cortex (OFC; BA 10) for the gamma, in the right supplementary motor area (BA 6) for the beta1, and in the right superior frontal gyrus (BA 8) for the beta2 frequency band extending into the right dorsal anterior cingulate cortex (dACC; BA 24). In contrast, delta band activity in the bilateral PCC (BA 31) and theta band activity in the right dorsal premotor cortex (BA 6) decreased significantly in the LOT group compared with that in the EOT group (Fig. 1).

3.1.2. The old control group versus the young control group

We further compared the old control group with the young control group to determine whether the differences between the LOT and EOT groups were actual tinnitus-related differences or merely differences based on normal aging. As illustrated in Fig. 2, sLORETA revealed overall decreased current densities in the old control group compared with the young control group. The starkest differences were decreased activities in the dACC (BA 24) for the theta, beta1, and beta2 bands (bilaterally for theta and left-sided for the beta1 and beta2 bands). In addition, the old control group demonstrated significantly decreased theta and alpha1 frequency band activity in the bilateral DLPFCs (BA 8). Moreover, decreased beta3 activity in the right posterior inferior temporal gyrus (BA 37) and gamma activity in the right secondary auditory cortex (A2; BA 21) were also observed in the old control group compared with the young control group.

3.1.3. The LOT group versus the old control group

When compared with the age- and sex-matched old control group, the LOT group showed increased beta2 activity in the left dACC. Significantly less delta activity in the left PCC (BA 30), beta3 in the right superior parietal lobule (BA 7), and gamma in the precuneus (BA 7) were observed in the LOT group compared with the control group. Additionally, decreased activities in the LOT group were also observed in the right OFC (BA 10) for alpha1 and left A1 (BA 42) for alpha2 frequency bands, respectively (Fig. 3).

3.1.4. The EOT group versus the young control group

Compared with the LOT and its control group, the EOT and the young control groups revealed fewer areas of significant differences. For the theta band, the EOT group demonstrated increased activity in the right DLPFC (BA 9) reaching the right dACC (BA 32) compared with the young control group. Conversely, the right DLPFC showed decreased beta1 activity in the EOT group compared with its control group (Fig. 4).

3.2. Functional connectivity analysis

3.2.1. The LOT group versus the EOT group

The functional connectivity analysis yielded significant differences between the LOT and EOT groups in the theta and alpha1 frequency bands ($p < 0.05$). The LOT group demonstrated increased lagged phase synchronization functional connectivity between bilateral A1s (BAs 41 and 42) and A2s (BAs 21 and 22) in the theta frequency band (Fig. 5A). In addition, the LOT group revealed increased functional connectivity compared with the EOT group between bilateral insulae in the alpha1 frequency band ($p < 0.05$). Furthermore, increased functional connections for alpha1 with marginal significance were found in the LOT group between the left insula and right subgenual ACC (sgACC), and between the right A2 and bilateral precunei (Fig. 5B).

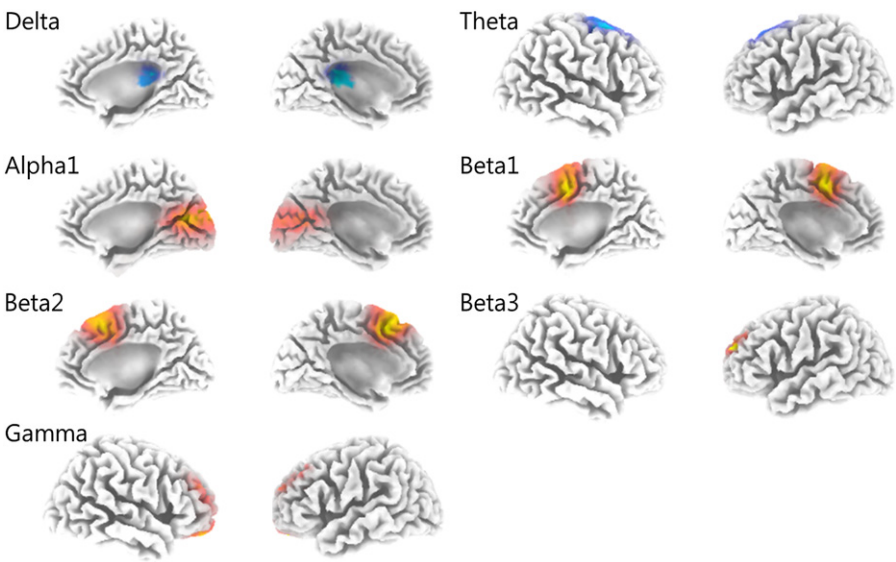

Fig. 1. Standardized low-resolution brain electromagnetic tomography contrast analysis between the late-onset tinnitus group and the early-onset tinnitus group. Compared with the early-onset tinnitus group, the late-onset tinnitus group showed increased activities in the prefrontal cortices and dorsal anterior cingulate cortex for beta3 and gamma and in the orbitofrontal cortex for gamma, but decreased activity in the posterior cingulate cortex for the delta frequency band.

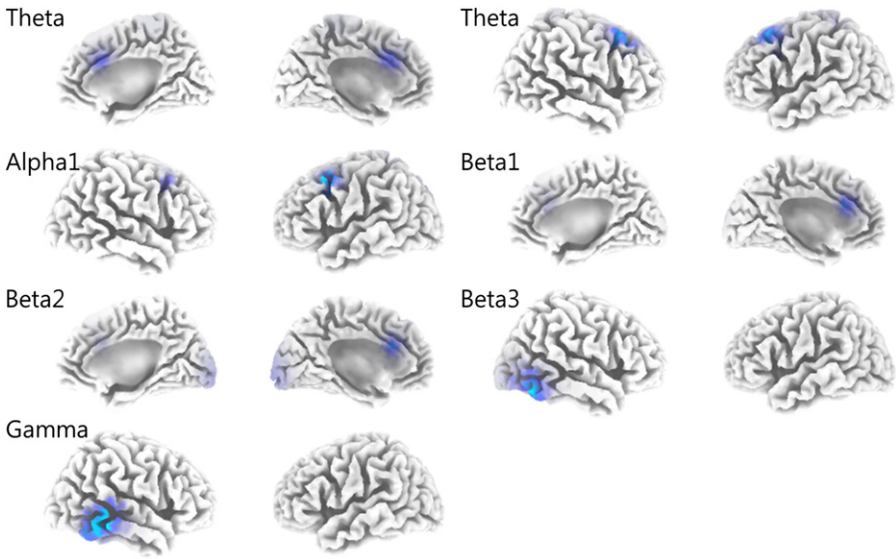

Fig. 2. Standardized low-resolution brain electromagnetic tomography contrast analysis between the old and young control groups. Compared with the young control group, the old group showed decreased activities in the dorsal anterior cingulate cortex for theta, beta1, and beta2, in the dorsolateral prefrontal cortex for theta and alpha1, in the right posterior inferior temporal gyrus for beta3, and in the right primary auditory cortex for the gamma frequency bands.

3.2.2. The old control group versus the young control group

In contrast to the increased functional connectivity between the right A2 and bilateral precunei by the contrast of "the LOT group minus the EOT group", a comparison of functional connectivity between the old and young control groups yielded significantly decreased functional connectivity between the right PCC and A1 in old control participants for the gamma frequency band ($p < 0.05$). Moreover, the old control group demonstrated a marginally significant decrease between the left PCC and right A1 ($0.05 < p < 0.06$) (Fig. 6).

For the other 7 frequency bands, no significant differences could be obtained between the 2 control groups in the contrast analysis of "the old control group minus the young control group".

3.2.3. Comparison of average weighted connectivity among the 4 groups

As illustrated in Fig. 7A, an ANOVA performed with the medial temporal lobe as a dependent variable and age and group as independent variables demonstrated a significant main effect for group ($F(1,114) = 3.98$, $p < 0.05$), but not for age ($F(1,114) = 0.604$, $p = 0.44$). Additionally, an interaction effect was obtained for age by group ($F(1,114) = 4.46$, $p < 0.05$). Further simple contrast analyses revealed that the young control group had significantly higher average weighted connectivity than the EOT group ($F(1,114) = 8.58$, $p < 0.05$), but no significant difference was observed between the old control and LOT groups ($F(1,114) = 0.01$, $p = 0.94$).

Another ANOVA conducted with PCC as a dependent variable and age and group as independent variables revealed a significant main effect for age ($F(1,114) = 4.15$, $p < 0.05$), but not group ($F(1,114) = 1.99$, $p = 0.16$). No significant interaction effect was observed for age by group ($F(1,114) = 0.44$, $p = 0.51$).

3.3. ROI analysis

The log-transformed mean current density for the delta frequency band at BA 41 in the LOT group (2.24 ± 0.54) was significantly higher than that of the old control group (1.88 ± 0.57) ($t = -2.471$, $p = 0.017$, $df = 55.87$). Similarly, the log-transformed

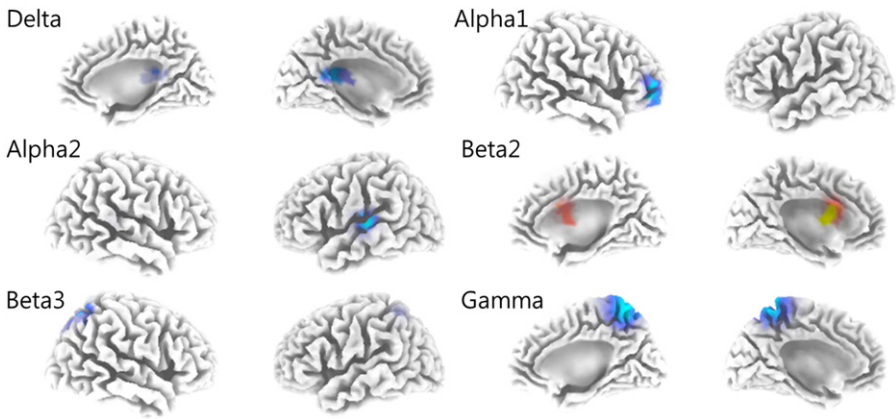

Fig. 3. Standardized low-resolution brain electromagnetic tomography contrast analysis between the late-onset tinnitus group and its old control group. Compared with the control group, the late-onset tinnitus group showed increased activity in the left dorsal anterior cingulate cortex for beta2, but decreased activities in the left posterior cingulate cortex for delta, in the right superior parietal lobule for beta3, in the precuneus for gamma, and in the right orbitofrontal cortex and left primary auditory cortex for the alpha bands.

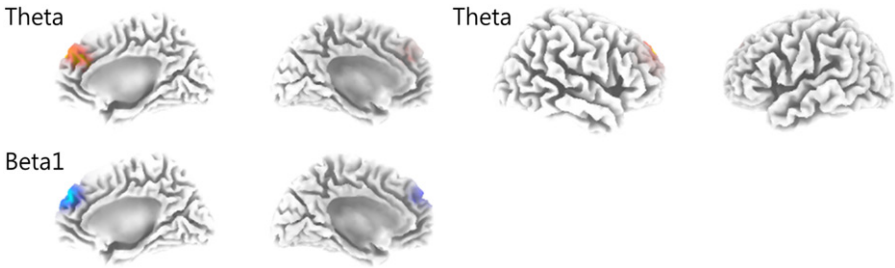

Fig. 4. Standardized low-resolution brain electromagnetic tomography contrast analysis between the early-onset tinnitus group and its control group. The early-onset tinnitus group demonstrates increased theta and decreased beta activities in the right dorsolateral prefrontal cortex compared with those in the control group.

mean current density for the delta frequency band at BA 42 in the LOT group (2.42 ± 0.82) was significantly higher than that of the old control group (1.89 ± 0.69) ($t = -3.314$, $p = 0.002$, $df = 55.64$) (Fig. 8). Therefore, we found significantly higher activation of the left A1 in the LOT group relative to its control group for the ROI analysis, although the difference was not significant in the sLORETA whole brain analysis.

4. Discussion

Recent examinations of normal healthy aging have revealed that anatomical and functional changes in the brain occur as we age and might be, at least partly, responsible for the age-related decline in cognitive functions (Backman et al., 2006; Raz and Rodrigue, 2006). Total brain volume declines with age (Giedd et al., 1999), with markedly accelerated loss in the insula, superior parietal gyri, central sulci, cingulate sulci, caudate, cerebellum, hippocampus, and the association cortices (Good et al., 2001; Raz et al., 2005). Atrophy has been documented for gray and white matter (Fjell et al., 2009; Hutton et al., 2009), and a loss of synaptic connections (Hutton et al., 2009). From a functional perspective, the anterior and/or subgenual cingulate cortices and the frontal cortices manifest the greatest aging-related deterioration with regard to regional metabolism measured by fluorodeoxyglucose positron emission tomography (Kalpouzos et al., 2009; Pardo et al., 2007; Volkow et al., 2000). Moreover, recent studies addressing functional connectivity have found aging-related decreased connectivity in the "default mode network" (DMN) consisting of the retrosplenial cortex, PCC, ventral prefrontal cortices (PFCs), precuneus, and angular gyrus, and in the "dorsal attention network" (DAN) consisting of the PFC, anterior cingulate, and posterior parietal cortices (Schlee et al., 2012; Tomasi and Volkow, 2012). Our results indicating decreased activities in the dACC for theta, beta1, and beta2 frequency bands and in the bilateral DLPFCs for theta and alpha1 frequency bands by the contrast of "the old control group minus the young control group" are consistent with previous studies in that the DAN components were relatively deactivated in the old control group. In addition, decreased connectivity between the PCC and auditory cortices in the old control group replicated our aforementioned previous observations of decreased connectivity in the DMN. Thus, we demonstrated that the control subjects followed the normal aging processes and that our quantitative electroencephalography measurements and interpretations solidly replicated our previous findings.

Our primary interest in the current study was to explore if there were any differences in the neural correlates associated with tinnitus between LOT and EOT individuals. That is, analogous to the cortical changes observed during normal healthy aging, we expected different pathophysiological mechanisms involved in a common symptom such as tinnitus between the different age of onset groups. Indeed, we found significantly increased activities in the prefrontal cortices for beta1, beta2, beta3, and gamma frequency bands, and in the dACC for beta1 and beta2 bands (Fig. 1) in the LOT group compared with the EOT group. These results were in sharp contrast with those from an analysis between the old and young control groups in the current study, and in previous studies of healthy elderly participants revealing deactivated prefrontal and anterior cingulate cortices. The tendency for dACC activation in the LOT group was supported when we compared it with the age- and sex-matched control group in that relative activation of the dACC was demonstrated for the beta2 band (Fig. 3), and the PCC, precuneus, and superior parietal lobule revealed relative deactivation for other frequency bands. Functional connectivity analyses further yielded significantly increased lagged-phase synchronization functional connectivity between bilateral A1s and A2s for the theta frequency band, and between bilateral insulae for the alpha1 frequency band in the LOT group compared with the EOT group. In addition, increased functional connectivity with marginal significance was found in the LOT group between the left insula and right sgACC, and between the right A2 and bilateral precunei. The latter contrasted with the observed decreased connectivity between the right A1 and bilateral PCCs in the old control groups compared with the young control group in the current study, and in previous studies showing decreased functional connectivity to the precunei.

From the viewpoint of described functional networks, participants with LOT activated components of DAN, such as the PFCs and the dACC. The increased activity in the dACC and increased connectivity to bilateral insulae might indicate activation of the intrinsic alertness network (IAN) (Fox et al., 2005; Fransson, 2005) in the LOT group. Moreover, although the components of the DMN, such as the PCC and the precuneus, manifested as relative deactivation, the tendency for increased functional connectivity to bilateral precunei implies differences in the DMN of the LOT group compared with the EOT group or the old control group. Therefore, we might describe the characteristics of the cortical changes in participants with LOT as "activation of the components of DAN and IAN, and changes in the DMN" (Fig. 9).

Previous studies on tinnitus have suggested that the amount of tinnitus-related distress is related to alpha and beta activity in a network consisting of the sgACC extending to the ventromedial prefrontal cortex and/or OFC, dACC, with the insula extending into the medial temporal lobe, the amygdala and/or hippocampal area, and the parahippocampus (De Ridder et al., 2011b; Vanneste et al., 2010a). The areas involved in tinnitus-related distress are analogous to the areas of affective aspects of pain processing (Craig, 2002; Peyron et al., 2000), posttraumatic stress disorder (Vermetten et al., 2007), and even the general emotional network (Critchley, 2005; Phan et al., 2002). These areas were in better agreement with activated areas in the LOT group than in the EOT

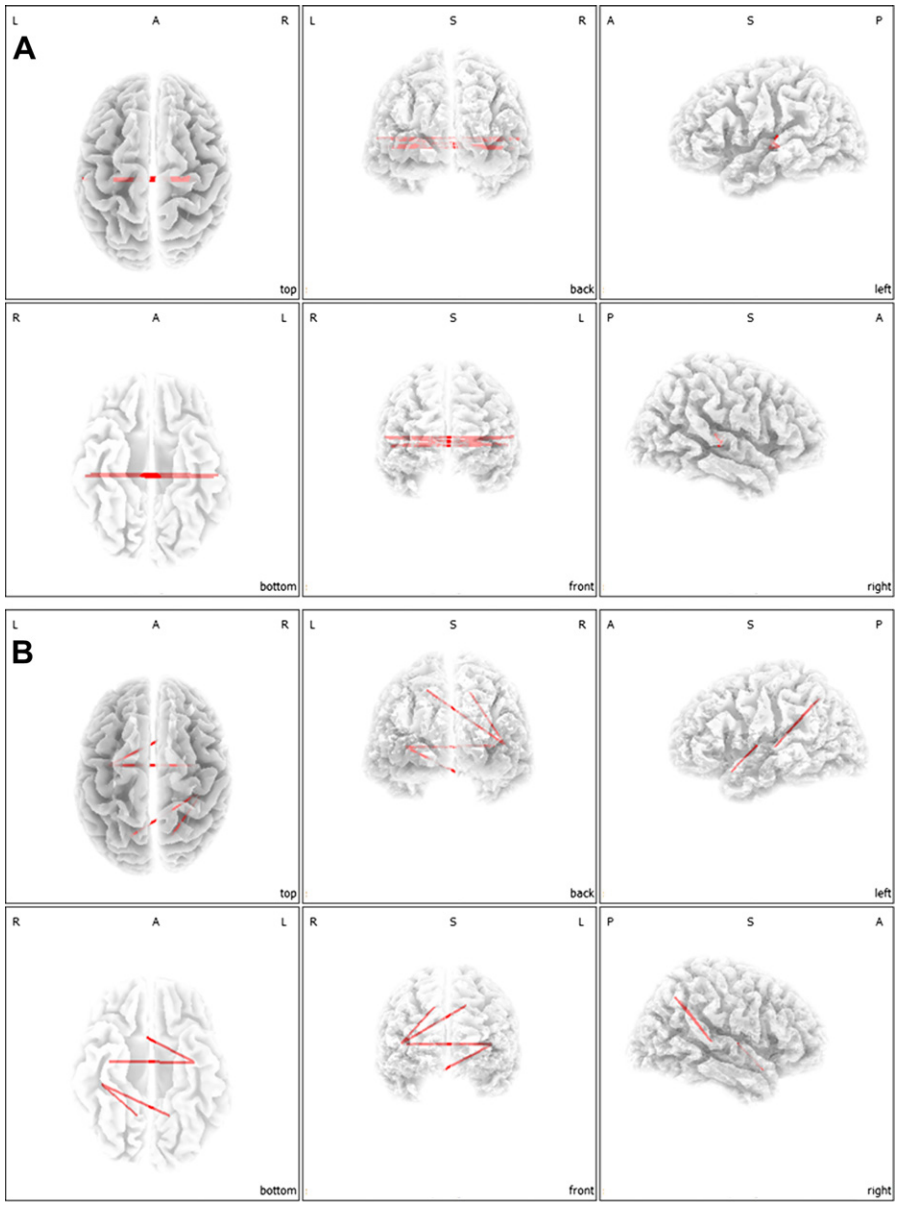

Fig. 5. Connectivity contrast analysis between the late-onset tinnitus group and the early-onset tinnitus group. Increased lagged connectivity between bilateral auditory cortices for theta and between bilateral insulae (A) and, with marginal significance, between the right insula and the left subgenual anterior cingulate cortex, and between the right secondary auditory cortex and bilateral precunei for the alpha1 frequency band in the late-onset tinnitus group compared with the early-onset tinnitus group (B). Abbreviations: L, left; A, anterior; R, right; P, posterior, S, superior.

group. Namely, relative activation of the OFC, DLPFC, and dACC, and increased insula–insula and insula–sgACC functional connectivity was more pronounced in the LOT group than in the EOT group. Thus, even with the same amount of distress, elderly patients with late tinnitus onset activate previously described distress-related areas more so than their younger counterparts with the same distress level and symptom duration. However, at this stage we cannot conclude that LOT patients are distressed because of these distress-related areas, because these cortical activities resulted from a comparison between 2 groups with the same amount of distress. In other words, because the LOT and EOT groups were near perfectly matched for known influencing factors, the relative activation pattern found in the LOT group was not associated with tinnitus sound or tinnitus-related distress, but it likely designates an age-related cortical activity pattern in LOT participants. However, other possible influencing factors that could explain the increased activation of the distress network in LOT patients should be evaluated in future studies. For example, older patients are more likely to have comorbidities which are also age-related, such as pain, cardiac, or respiratory problems. These comorbidities could also activate the same distress network because the distress network is most likely nonspecific (De Ridder et al., 2011b; Moazami-Goudarzi et al., 2010; Schnupp, 2011). Even though the tinnitus-related distress is the same in the LOT and EOT groups (based on the Tinnitus Questionnaire) the total distress might be higher in the LOT group because of distressing comorbidities. A future study should also try to control for depression, analogous to the differences between men and women in tinnitus (Vanneste et al., 2012). Women develop more mood changes, as measured by the Beck Depression Inventory-II for the same tinnitus loudness, the same distress, and the same tinnitus type than men, and this is associated with orbitofrontal and prefrontal cortex beta activity

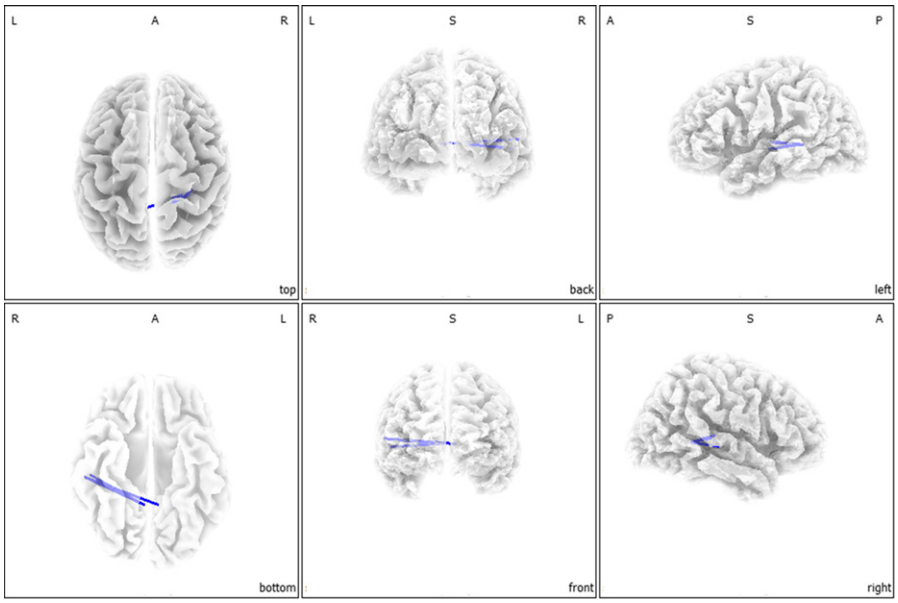

Fig. 6. Connectivity contrast analysis between the old and young control groups. Decreased lagged connectivity between the right primary auditory cortex and bilateral posterior cingulate cortices for the gamma frequency band in the old control group compared with the young control group. Abbreviations: L, left; A, anterior; R, right; P, posterior, S, superior.

changes (Vanneste et al., 2012). Furthermore, investigations comparing high and low distress in LOT and EOT subgroups might be helpful to understand the exact role of this characteristic activation.

The tendency of distress network-centered activation in the LOT group might be of value from a therapeutic point of view. For instance, recent studies have suggested that transcranial magnetic stimulation (TMS) using a double-cone coil (DCC) can modulate the dACC and sgACC (Hayward et al., 2007), and that frontal TMS using a DCC is capable of suppressing tinnitus transiently depending on the repetitive TMS frequency used (Vanneste et al., 2011). However, based on the results of the current study, we hypothesize that DCC-based frontal TMS might yield better results in patients with LOT than those with EOT. Of course this treatment cannot be dichotomized because of the diverse nature of tinnitus. If all other clinical characteristics such as the nature of the tinnitus, duration of symptoms, and Tinnitus Questionnaire score are identical, we might expect more of an effect from a LOT patient than from an EOT patient using this treatment modality.

The young control group showed significantly higher weighted connectivity compared with the EOT and old control groups for the medial temporal lobe and PCC. In contrast, the weighted connectivity comparison revealed no significant difference between the LOT and EOT groups or between the LOT group and the old control group for these areas. In this regard, we might surmise that decreased functional connectivity in these areas might be characteristics of EOT. One discrepancy between our results and the aforementioned study by Schlee et al. (2012) is that our data show increased connectivity for the medial temporal lobe in the young control subjects whereas Schlee et al. showed age-related increased inflow to the medial temporal lobe. This discrepancy seems to originate from a difference in methods, because we used linear lagged functional connectivity, which does not measure directionality such as inflow or outflow.

Another interesting finding of the current study was the difference between the LOT group and the old control group with regard to activation of the left A1. That is, when compared with the control group, the LOT group demonstrated decreased activation for alpha1 in the sLORETA whole brain analysis and increased activation for delta frequency band in the left A1 ROI analysis. These findings agree with a previous study revealing marked reduction for alpha power together with an enhancement for delta in tinnitus participants (Weisz et al., 2005a). Again, these

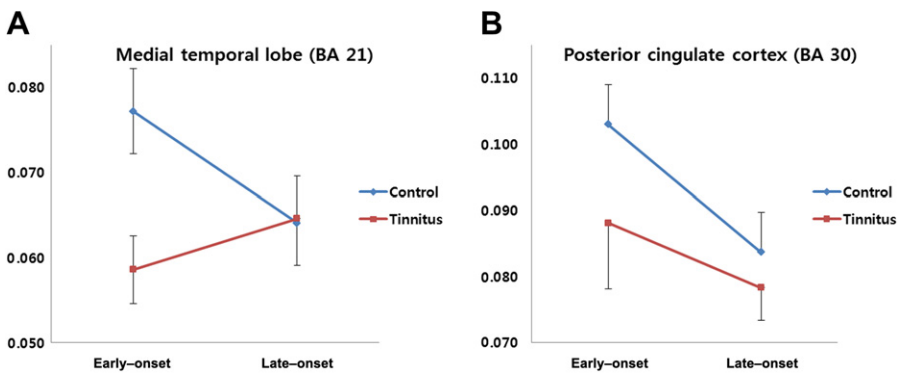

Fig. 7. Comparison of average weighted connectivity of the medial temporal lobe and posterior cingulate cortex among the 4 groups. Abbreviation: BA, Brodmann area.

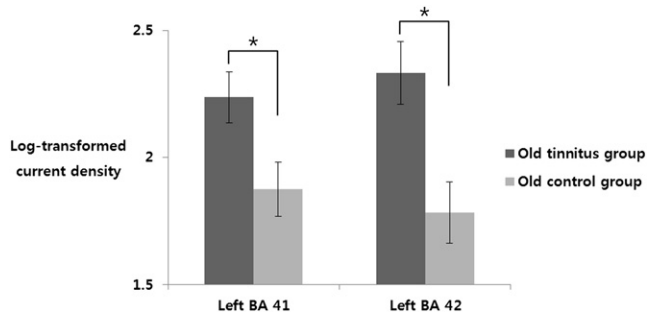

Fig. 8. Region of interest analysis for the left primary auditory cortex for the delta frequency band. Log-transformed mean current densities of the late-onset tinnitus group were significantly higher than its old control group (asterisks). Error bars designate standard errors. Abbreviation: BA, Brodmann area.

differences might indicate different characteristics of LOT compared with EOT, because these differences in the auditory cortex were not observed in the comparison between the EOT group and its young control group. These differences might be because of a higher neuroplastic potential in the EOT group than in the LOT group; thus, the EOT group might recover better than the LOT group from typical neuroplastic changes in the auditory cortex (Schlee et al., 2011).

Several limitations of the study have to be mentioned. First, we strictly recruited NBN bilateral patients to ensure homogeneity of the study participants. However, a recent study has proposed activity differences in the PFC and PCC between NBN and pure-tone tinnitus (Vanneste et al., 2010b). Because these were the areas of the main differences between the LOT and EOT groups, the results might have been partially affected at the stage of participant recruitment. Therefore, a further study with pure-tone tinnitus participants might be of importance. Second, another recent study has suggested that right anterior insular activity is correlated with tinnitus-related distress partly mediated by orthosympathetic tone (OT) (van der Loo et al., 2011). Because no OT measurement was performed in the study participants and control subjects, the difference in functional connectivity to the insula might have partially been biased by potential differences in OT.

This is the first study to compare brain changes associated with tinnitus based on the age of onset. Differences with regard to the age of tinnitus onset might be applicable to various future studies on other similar pathologies. Tinnitus distress networks share commonly activated areas with other pathologies such as pain, posttraumatic stress disorder, or depressive disorder. Inasmuch as these diseases show analogies to tinnitus, we might surmise that future studies on these pathologies might also reveal some differences in disease-related brain activation with regard to the age of onset, which might be applicable for different approaches to treatment. In this regard, this study could be a stepping stone for such studies.

Taken together, the characteristics of the participants with later onset tinnitus could be described as activation of previously described distress-related areas and the DAN and IAN components. In other words, we observed increased activation of previously suggested tinnitus-related distress networks, and changes in the DMN compared with earlier onset tinnitus patients with the same distress level and symptom duration. The findings of intrinsic differences between these groups, such as normal changes of healthy aging, might be applicable for understanding pathophysiological differences between earlier and later onset tinnitus and also for planning individualized treatment modalities.

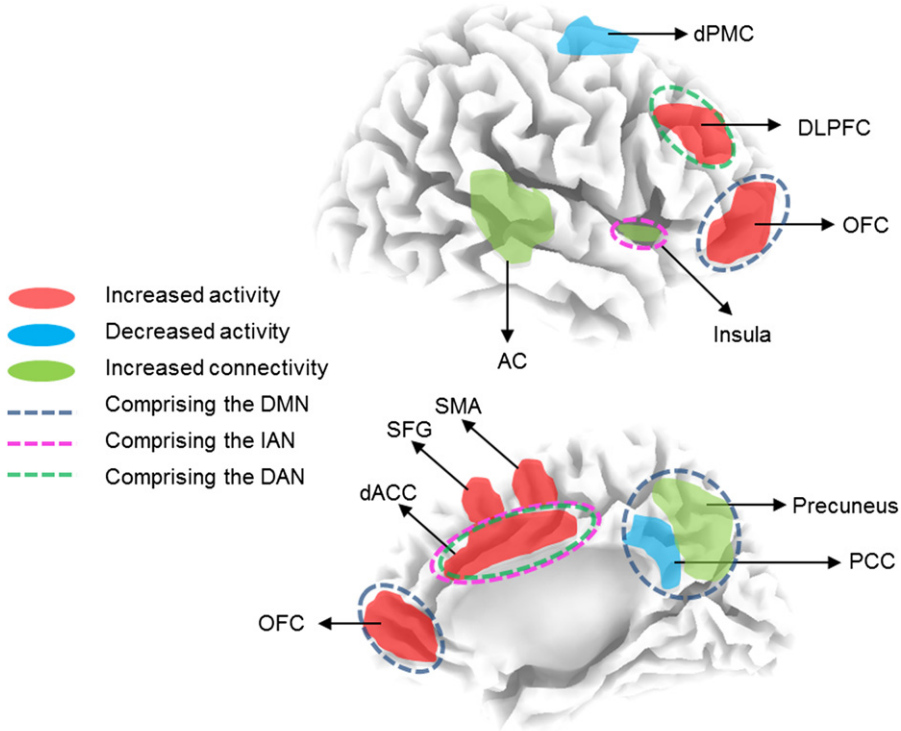

Fig. 9. Schematic summary of the areas with increased or decreased activities. Increased functional connectivity in the late-onset tinnitus group compared with the early-onset tinnitus group. Dotted ellipses designate areas comprising the default mode, intrinsic alertness, and dorsal attention networks (DMN, IAN, and DAN, respectively). Abbreviations: AC, auditory cortex; dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; DMN, default mode network; dPMC, dorsal premotor cortex; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; SFG, superior frontal gyrus; SMA, supplementary motor area.

Disclosure statement

The authors disclose no conflicts of interest.

This study was approved by the local ethical committee at Antwerp University Hospital and was in accordance with the Declaration of Helsinki. Participants gave oral informed consent before the procedure. The EEG was obtained as a standard procedure for diagnostic and neuromodulation treatment purposes.

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