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ORIGINAL ARTICLE

Onset-related differences in neural substrates of tinnitus-related distress: the anterior cingulate cortex in late-onset tinnitus, and the frontal cortex in early-onset tinnitus

Jae-Jin Song · Sven Vanneste · Winfried Schlee · Paul Van de Heyning · Dirk De Ridder

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Abstract Recent findings regarding differences in tinnitus-related neural activity according to onset age have raised a question on possible onset age-related differences in neural substrates of distress. Hence we collected quantitative electroencephalography (qEEG) findings of 28 late-onset tinnitus (LOT) and 29 early-onset tinnitus (EOT) (mean onset age 52.3 and 29.0 years, respectively) participants. According to the tinnitus questionnaire (TQ) score grade, LOTs were then subdivided into 13 high distress (HD; TQ grade 3 or 4) and 15 low distress (LD; TQ grade 1 or 2), while EOTs into 14 HD and 15 LD. Compared to the EOT group, the LOT group demonstrated increased qEEG source-localized activity and functional connectivity primarily in the anterior cingulate cortex (ACC) and parahippocampus. In subgroup comparisons, the ACC was activated more in HD–LOT participants than in LD–LOT participants for the beta 1, beta 2 and gamma frequency bands, while the left orbitofrontal cortex and left dorsolateral prefrontal cortex were activated more in HD–EOT than in LD–EOT for the delta/beta and gamma frequency bands, respectively. Even with the same amount of tinnitus-related distress level, responsible neural substrates are different according to the onset age. These differences may be important for exploring different target areas of treatment according to tinnitus onset age, as well as for conducting similar studies on other pathologies, such as depression or pain.

Keywords Tinnitus · Anxiety · Aging · Electroencephalography · Gyrus cinguli · Prefrontal cortex

J.-J. Song (✉)
Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University Hospital, Yun-Kun Dong 28, Chong-No Gu, Seoul 110-744, Korea
e-mail: jjsong96@gmail.com

S. Vanneste · P. Van de Heyning
Department of Translational Neuroscience, Faculty of Medicine, University of Antwerp, Antwerp, Belgium

W. Schlee
Institute for Psychology and Education, University of Ulm, Ulm, Germany

P. Van de Heyning
Department of Otorhinolaryngology and Head and Neck Surgery, University Hospital Antwerp, Edegem, Belgium

D. De Ridder
Section of Neurosurgery, Department of Surgical Sciences, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand

Introduction

Subjective tinnitus, a phantom sound perception without an identifiable sound source (Jastreboff 1990), afflicts 5–25 % of the general population, and tinnitus-related distress severely affects quality of life in 1 % of the population (Axelsson and Ringdahl 1989; Khedr et al. 2010). Alongside protracted life expectancy and raised interest in quality of life, tinnitus has become more problematic due to the prevalence of chronic tinnitus being higher in the geriatric population Shargorodsky et al. (2010), and especially higher in more recent birth geriatric cohorts. This is most likely a result of increased prevalence, increased awareness of symptoms, and/or higher health expectations (Nondahl et al. 2012).

Late-onset tinnitus (LOT) was recently found to differ from early-onset tinnitus (EOT) with regard to tinnitus-related distress, in that LOT is more abruptly and severely

distressing than EOT (Schlee et al. 2011). This raised a question on possible differences in the neural substrates of tinnitus between LOT and EOT individuals, as understanding these potential differences may be a prerequisite for adopting individualized treatment. Inasmuch as neuroplastic processes play a crucial role in tinnitus generation and related distress, neural correlates involved in tinnitus-related distress may be different between the LOT and EOT groups, since normal aging itself is associated with functional disruption, under-recruitment, and subsequent compensatory recruitment of cortical networks (Logan et al. 2002; Davis et al. 2008). Indeed, a recent study demonstrated with certainty intrinsic activity and functional connectivity differences in areas such as the prefrontal cortex, dorsal anterior cingulate cortex (dACC), and insula between the late- and early-onset narrow band noise (NBN) tinnitus groups (Song et al. 2013a). However, because the two groups in Song et al. study were strictly matched for distress level, namely tinnitus questionnaire (TQ) score (Goebel and Hiller 1994), we do not exactly know the role of these cortical activity differences in tinnitus-related distress. Also, our previous findings in NBN tinnitus may be generalizable only if it is replicated in other types of tinnitus, such as pure-tone tinnitus.

Therefore, to resolve the obscurity of differences with regard to the age of symptom onset, it was essential to perform another study examining the differences in the neural substrates associated with tinnitus between high distress (HD) and low distress (LD) subgroups of both the late- and early-onset pure-tone tinnitus groups. By matching affecting factors for tinnitus as much as possible, excluding TQ scores, we could compare distress-related differences between the HD–LOT and LD–LOT subgroups and between the HD–EOT and LD–EOT subgroups, and achieve our stated aim of localizing the neural substrates of high distress for both the LOT and EOT groups separately. Moreover, by recruiting only pure-tone tinnitus participants, we further investigated if our previous findings of cortical activity differences in NBN tinnitus can be solidly replicated in other types of tinnitus. By performing the current study, we attempted to clarify the unique sources of distress according to the age of tinnitus onset and the possibility of individualized treatment according to the age of tinnitus onset. Henceforth, we describe the results of our source-localized quantitative electroencephalography (qEEG) analysis.

Methods and materials

Participants

To investigate replicability of our pervious findings on onset-related cortical activity differences in NBN tinnitus, as well as to maintain homogeneity of the participants with regard to tinnitus sound characteristics, we selected individuals only with bilateral (subjectively perceivable in both ears) pure-tone tinnitus from the database of multidisciplinary Tinnitus Research Initiative Clinic of the University Hospital of Antwerp, Belgium. We excluded individuals with pulsatile tinnitus, otologic disorders such as otosclerosis and Ménière's disease, chronic headache, hearing loss exceeding the range of serviceable hearing (40 dB) (Farrior 1956) in at least one ear, psychiatric or neurological disorder, current psychotropic/central nervous system-active medications, history of drug/alcohol abuse, and/or history of head injury (with loss of consciousness) or seizures. In this way, 57 participants with bilateral pure-tone tinnitus ($N = 57$; 49 males and 8 females) with an average age of 45.6 ± 14.6 years (range 16–67) were included in the study.

In addition, to investigate basic differences between age groups and explore contributions of the normal aging process to any differences between the LOT and EOT groups, 57 individuals who did not have either tinnitus or hearing loss greater than 40 dB HL were collected from a normative database consisting of 235 participants who underwent an EEG analysis. We were, therefore, able to match the tinnitus participants and the controls with regard to age and sex, which resulted in a control group consisting of 47 males and 10 females with a mean age of 46.6 ± 16.9 years (range 18–78 years).

Subgrouping of the tinnitus subjects

In order not to obtain biased subgroups, previously reported factors that influence activity in the tinnitus brain were strictly matched in the initial stage of participant recruitment. As a result, of the 57 participants, 28 with a mean onset age (the age ever since the person noticed his/her tinnitus) 52.3 ± 4.3 years were allocated to the LOT group, and the other 29 with a mean onset age 29.0 ± 10.1 were allocated into the EOT group, with no significant differences between the two groups for sex, tinnitus duration, Numeric Rating Scale (NRS) intensity, NRS distress, anxiety and depression level measured by Hospital anxiety and depression scale (HADS) (Bjelland et al. 2002), or total TQ score evaluated by the validated Dutch version of the TQ (Meeus et al. 2007) (Table 1). Tinnitus loudness (intensity) and frequency matching tests were performed contralateral to the worst tinnitus ear as all the participants were bilateral pure-tone tinnitus patients (Meeus et al. 2010). No significant differences were found for hearing threshold between the 2 groups, as determined by the mean value of pure-tone audiometry thresholds at 0.5, 1, and 2 kHz (Song et al. 2009; Mirandola et al. 2013; Song et al. 2012b) and the loss in decibels (dB HL) at the tinnitus

Table 1 Overall characteristics of the late- and early-onset tinnitus groups

	Late-onset tinnitus group ($n = 28$)	Early-onset tinnitus group ($n = 29$)	p values
Age (years)	57.7 ± 4.8	33.9 ± 10.7	<0.01
Age of onset (years)	52.3 ± 4.3	29.0 ± 10.1	<0.01
Male:female	24:4	25:4	–
Tinnitus duration (years)	5.5 ± 5.1	4.9 ± 4.4	0.66
Total score on tinnitus questionnaire	43.7 ± 25.1	43.1 ± 24.9	0.93
Hearing threshold (dB HL)	22.3 ± 6.4	19.8 ± 7.0	0.17
Hearing threshold at TF (dB HL)	30. 4 ± 10.3	26.7 ± 10.1	0.18
NRS intensity	6.1 ± 2.4	5.6 ± 2.4	0.48
NRS distress	6.1 ± 3.0	5.8 ± 2.7	0.66
HADS depression score	8.6 ± 5.1	8.9 ± 5.2	0.84
HADS anxiety score	8.0 ± 5.2	7.9 ± 5.8	0.94

TF tinnitus frequency, *NRS* numeric rating scale, *HADS* hospital anxiety and depression scale

frequency (Table 1). Therefore, possible cortical activity differences between the two groups due to differences in hearing thresholds could be minimized. In addition, no significant differences in age or sex were found between the LOT and the old control group, or between the EOT and the young control group.

The two groups were then subdivided according to TQ scores. Participants with a TQ score of 0–46 (grade 1 or 2) were allocated to LD subgroups, while those with 47–84 (grade 3–4) were allocated to HD subgroups. In this way, a total of four subgroups (HD–LOT, LD–LOT, HD–EOT, and LD–EOT) were created. Again, the subgroups in the LOT and EOT groups were matched for possible affecting factors as much as possible, with the exception of TQ score. In other words, between both the HD–LOT and LD–LOT subgroups, and the HD–EOT and LD–EOT subgroups, no significant differences were found in age, tinnitus duration, age of onset, sex, or hearing threshold (Table 2). Also, between the HD–LOT and HD–EOT subgroups and LD–LOT and LD–EOT subgroups, except for the mean age and the mean age of tinnitus onset, no significant differences were found in affecting factors such as TQ score, anxiety and depression level measured by HADS, tinnitus duration, sex, or hearing threshold (Table 2).

EEG recording

This study was approved by the Institutional Review Board at Antwerp University Hospital ('Comité voor medische ethiek') and was in accordance with the declaration of Helsinki. Patients gave informed consent before the EEG recording. The EEG is obtained as a standard procedure for diagnostic and neuromodulation treatment purposes.

Participants abstained from alcohol consumption 24 h prior to EEG recording and from caffeinated beverages on the day of recording to avoid alcohol-induced changes in EEG (Volkow et al. 2000) or a caffeine-induced alpha power decrease (Logan et al. 2002; Gates and Cooper 1991). The vigilance of participants was monitored by EEG parameters such as the slowing of alpha rhythm or the appearance of spindles, as drowsiness is reflected in enhanced theta power (Moazami-Goudarzi et al. 2010).

EEGs were recorded for approximately 5 min using a Tin-electrode cap (ElectroCap, Ohio, United States) and Mitsar amplifier (Mitsar EEG-201, St.Petersburg, Russia) in a fully lighted room which was shielded from sound and stray electric fields, with each participant sitting upright in a comfortable chair. The EEG was sampled with 19 electrodes in the standard 10–20 International placement, referenced to linked ears, and impedances were checked to remain below 5 kΩ at all electrodes throughout the EEG recording. Data were collected with the subjects' eyes closed (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). The data were then resampled to 128 Hz, band-pass filtered using fast Fourier transform filter (2-s epochs with 50 % overlapping by the use of Hanning time window) to 2–44 Hz and subsequently transposed into Eureka! software (Sherlin and Congedo 2005). Finally, the data were plotted and carefully inspected for artifact rejection. All episodic artifacts including eye blinks, eye movements, teeth clenching, body movement, or electrocardiogram artifact were removed manually from the EEG stream. In addition, an independent component analysis (ICA) was conducted to further verify if all artifacts had been excluded. To investigate the effect of possible ICA component rejection, we compared the power spectra with two approaches: (1) after visual artifact rejection only, and (2) after 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 (30.5–44 Hz) bands (Song et al. 2013a, b, c) did not show a statistically significant difference between the two approaches. We were, therefore, confident in reporting the results of two-step artifact correction data, namely visual-artifact rejection and additional independent component rejection. Average Fourier cross-spectral matrices were computed for all eight bands.

Source localization analysis

Standardized low-resolution brain electromagnetic tomography (sLORETA) was utilized to estimate the

Table 2 Overall characteristics of the four subgroups

	Late-onset tinnitus			Early-onset tinnitus		
	High distress ($n = 13$)	Low distress ($n = 15$)	p values	High distress ($n = 14$)	Low distress ($n = 15$)	p values
Age (years)	58.3 ± 5.9	57.2 ± 3.8	0.55	33.9 ± 11.3	34.0 ± 10.6	0.97
Onset (years)	52.7 ± 5.3	51.9 ± 3.3	0.47	29.0 ± 10.2	29.1 ± 10.3	0.99
Male:female	11:2	13:2	–	11:3	14:1	–
Duration (years)	5.6 ± 5.2	5.3 ± 5.3	0.87	4.9 ± 5.6	4.9 ± 3.1	0.96
Total TQ score	69.2 ± 5.7	21.5 ± 7.5	<0.01	67.7 ± 6.5	20.1 ± 5.5	<0.01
HT (dB HL)	22.9 ± 6.0	21.8 ± 6.9	0.67	21.8 ± 6.5	18.0 ± 7.1	0.15
HT-TF (dB HL)	32.3 ± 12.8	28.1 ± 6.0	0.28	28.0 ± 12.8	25.5 ± 7.1	0.51
NRS intensity	7.7 ± 1.0	4.7 ± 2.4	<0.01	6.3 ± 3.1	5.0 ± 1.5	0.16
NRS distress	8.5 ± 0.8	4.1 ± 2.7	<0.01	7.8 ± 2.4	4.0 ± 1.3	<0.01
HADS-DS	13.3 ± 3.0	4.5 ± 2.2	<0.01	13.4 ± 2.5	4.4 ± 2.5	<0.01
HADS-AS	12.8 ± 3.0	3.9 ± 2.3	<0.01	13.2 ± 2.0	2.6 ± 2.4	<0.01

Duration tinnitus duration, *TQ* tinnitus questionnaire, *HT* hearing threshold, *HT-TF* hearing threshold at tinnitus frequency, *NRS* numeric rating scale, *HADS* hospital anxiety and depression scale, *DS* depression score, *AS* anxiety score

intracerebral sources generating the scalp-recorded electrical activity in each of the eight frequency bands (Pascual-Marqui 2002). The sLORETA technique computes electric neuronal activity as current density (A/m^2), without assuming a predefined number of active sources. The sLORETA solution space comprises 6,239 voxels (voxel size: 5 × 5 × 5 mm) and is restricted to cortical gray matter and hippocampi, as defined by the digitized MNI152 template (Fuchs et al. 2002). Scalp electrode coordinates on the MNI brain are derived from the international 5 % system (Jurcak et al. 2007). The accuracy of the sLORETA approach has been repeatedly validated from studies comparing sLORETA with other established localization methods such as structural magnetic resonance imaging (MRI) (Worrell et al. 2000), functional fMRI (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 the localization findings obtained from previous studies using invasive, implanted depth electrodes for epilepsy (Zumsteg et al. 2006a, c) and cognitive ERPs (Volpe et al. 2007) as reasonable evidence. In addition, previous studies have shown accurate localization of deep brain structures such as the ACC (Pizzagalli et al. 2001) and the mesial temporal lobe (Zumsteg et al. 2006b) using sLORETA.

Functional connectivity

Phase synchronization over multiple frequency bands is suggested to be the most plausible mechanism of large-scale neuronal integration overcoming the distributed anatomical and functional organization of brain activity to enable coherent behavior and cognition (Varela et al. 2001). However, any method of phase synchronization measurement is highly contaminated with an instantaneous, non-physiological contribution due to volume conduction and low spatial resolution (Bruder et al. 2012). To resolve this problem, a refined technique (i.e., Hermitian covariance matrices) that removes this confounding factor considerably has recently been introduced (Pascual-Marqui 2007). As such, this measure of dependence can be applied to any number of brain areas jointly, i.e., distributed cortical networks, whose activity can be estimated with sLORETA. With this method, measures of linear dependence (coherence) between multivariate time series are defined and the coherences are expressed as the sum of lagged/instantaneous dependence. The measures are non-negative, and take the value zero only when there is independence of the pertinent type, defined in all eight frequency bands as described above. Following this principle, lagged connectivity was calculated using the connectivity toolbox in sLORETA. A total of 28 regions of interest (ROIs) for functional connectivity analysis were utilized based on previous literature on tinnitus, and detailed information of these 28 ROIs are described in Table 3. Each ROI consists of a single voxel (the one that is closest to the center of mass of the ROI) in sLORETA, therefore, the radius around each centroid is 5 mm.

Statistical analysis

To identify potential differences in brain electrical activity, voxel-by-voxel analysis using sLORETA was performed for each frequency bands between-condition comparisons of the current density distribution. Nonparametric statistical analyses of sLORETA images (statistical non-parametric mapping; SnPM) were performed for each contrast

Table 3 Twenty-eight regions of interest and their references

Regions of interest	BA	Centroid voxel*			References
		x	*y*	*z*	
Auditory cortices	41L	−46	−29	10	Jastreboff (1990), Kringelbach (2005), Rolls (2004), Hwang et al. (2009), Levitin et al. (2003), Song et al. (2012a)
	41R	47	−29	10	
	42L	−62	−23	12	
	42R	63	−24	12	
	21L	−57	−18	−15	
	21R	58	−17	−15	
	22L	−56	−25	5	
	22R	56	−22	3	
Insula	13L	−39	−8	9	De Ridder et al. (2011), Dias et al. (1996), Hwang et al. (2009)
	13R	40	−7	9	
Dorsal anterior cingulate cortex	24L	−8	2	36	De Ridder et al. (2011), Damasio (1996)
	24R	7	1	36	
Pregenual anterior cingulate cortex	32L	−9	29	21	De Ridder et al. (2011)
	32R	8	30	20	
Subgenual anterior cingulate cortex	25L	−8	18	−17	Vanneste et al. (2010a), De Ridder et al. (2011)
	25R	5	14	−14	
Posterior cingulate cortex	31L	−11	−50	32	Davis et al. (2008), Vanneste et al. (2010a) as well as source localization analysis results of the current study
	31R	9	−48	33	
Parahippocampus	27L	−19	−33	−4	Volz and von Cramon (2009), Hwang et al. (2009)
	27R	18	−33	−4	
	29L	−7	−50	7	
	29R	6	−50	8	
Orbitofrontal cortex	10L	−22	54	9	De Ridder et al. (2011), Vanneste et al. (2010a), Hwang et al. (2009), Mahoney et al. (2011)
	10R	22	54	9	
	11L	−18	43	−17	
	11R	19	43	−17	
Precuneus	7L	−17	−63	50	Vanneste et al. (2010a), Hwang et al. (2009) as well as source localization analysis results of the current study
	7R	15	−63	49	

BA Brodmann area, *L* left, *R* right

* Coordinates are described in MNI coordinates

using sLORETA-built-in voxelwise randomization tests (5000 permutations) and *t* statistics for independent groups ($p < 0.05$). The SnPM methodology does not rely on any Gaussian assumptions by employing a locally pooled (smoothed) variance estimate that can outperform the Statistical Parametric Mapping approach (Segrave et al. 2011). SnPM's permutation method for correction for multiple comparisons (5,000 permutations in the current study) has been proven similar to those obtained using a standard GLM approach with multiple comparisons corrections derived from random field theory (Holmes et al. 1996; Nichols and Holmes 2002).

To determine differences in lagged connectivity, between the HD–LOT and LD–LOT groups as well as between HD–EOT and LD–EOT groups for each contrast, we performed *t* statistics for independent groups with a corrected threshold $p < 0.05$, which were also corrected for multiple comparisons by conducting sLORETA-built-in voxelwise randomization tests (5000 permutations).

Region of interest analysis

Log-transformed electric current density was averaged across all voxels in each ROI. Each ROI was defined by a single voxel that was closest to the center of the area where a significant difference was found in the source localization analysis. These were the dACC (BA24), the pregenual anterior cingulate cortex (pgACC, BA32), the orbitofrontal cortex (OFC, BA10), and the dorsolateral prefrontal cortex (DLPFC, BA9). Region of interest analyses were conducted separately for each frequency band. For these ROIs, an analysis of variance (ANOVA) was performed with the age of onset and the level of distress as major independent variables, and log-transformed current density for each specific region of interest as the dependent variable to calculate main effect (the age of onset and the level of distress) and interaction effect (the age of onset X the level of distress).

A discriminant analysis was conducted to determine whether each region of interest can disclose if a tinnitus participant is highly distressed or not. Predictor variables were selected from the regions showing the most significant subgroup differences by way of source localization analysis. In this way, predictor activity for the LOT group was determined to be beta 1 and 2 activity in the dACC, and gamma frequency band the activity in the pgACC. While EOT group predictor activity was investigated for delta and beta1 bands in the OFC and gamma band activity in the DLPFC. In addition, the variables used for both the LOT and EOT groups were utilized for the whole 4 subgroup-level discriminant analysis to figure out the predictability of these variables on the whole subgroup level.

Results

Source localization analysis

The LOT group vs. the EOT group

First, a comparison was made between results obtained in the participants in the LOT and EOT groups. For the beta1 results from the LOT, the LOT group indicated significantly increased activities in the dACC (BA24) as compared with the EOT group. For the beta2 band we found significantly increased activity in the dACC, subgenual anterior cingulate cortex (sgACC, Brodmann area (BA) 25), and parahippocampus (PHC, BA 34) in the LOT group relative to the EOT group; and for the gamma band we found significantly increased activity in the right pgACC (BA 32) and DLPFC (BA9) in the LOT group as compared with the EOT group (Fig. 1). Thus, we have replicated most of the activated areas obtained by our previous study on NBN tinnitus (Song et al. 2013a).

The old control group vs. the young control group

We further compared the old and the young control groups to investigate whether the differences between the LOT and EOT groups are purely tinnitus-related or associated merely with normal aging. sLORETA demonstrated overall decreased current densities in old controls as compared with young controls. The decreased activity in the old control group was most prominent in the dACC (BA 32) theta, beta1, and beta2 bands (bilaterally for theta and left-sided for the beta1 and 2 bands), and in the bilateral DLPFCs (BAs 8 and 9) theta, alpha1, and beta 2 frequency bands (bilaterally for the theta and left-sided for the alpha1 and beta2 bands). Moreover, decreased beta3 activity in the right posterior inferior temporal gyrus (BA 37) and decreased gamma activity in the right secondary auditory cortex (A2, BA 21) were observed in the old control group when compared to the young control group (Fig. 2).

The HD–LOT subgroup vs. the LD–LOT subgroup

Relative to the LD–LOT subgroup, the HD–LOT subgroup demonstrated significantly increased activities in the dACC (BA 24) beta 1 and 2 frequency bands, and in the pgACC (BA 32) gamma frequency band (Fig. 3). A one-way ANOVA analysis among the four subgroups revealed significant effect in the dACC for the beta 1 and beta 2 bands ($df = 3$, $F = 3.57$, $p = 0.02$, and $df = 3$, $F = 3{,}61$, $p = 0.02$, respectively) and in the pgACC for the gamma band ($df = 3$, $F = 6.40$, $p < 0.01$) (Fig. 3, bar plots).

The HD–EOT subgroup vs. the LD–EOT subgroup

In contrast, when compared to the LD–EOT subgroup, the HD–EOT subgroup showed significantly increased activity in the left OFC (BA 10) for the delta, beta 1, beta 2, beta 3, and gamma frequency bands (Fig. 4). The HD–EOT group showed additional increased activities in the left supramarginal gyrus (SMG) (BA 40) for the alpha 1, and in the left DLPFC (BA 9) for the gamma frequency band (Fig. 4). A one-way ANOVA analysis among the four subgroups revealed significant effect in the left OFC (BA 10) for the delta, beta 1, beta 2, and beta 3 frequency bands ($df = 3$, $F = 4.91$, $p < 0.01$, $df = 3$, $F = 4.79$, $p < 0.01$, $df = 3$, $F = 3.87$, $p < 0.01$, and $df = 3$, $F = 4.69$, $p < 0.01$, respectively), in the left SMG for the alpha1 band ($df = 3$, $F = 3.61$, $p = 0.02$), and in the left DLPFC for the gamma frequency band ($df = 3$, $F = 3.87$, $p = 0.01$) (Figs. 4, 5, bar plots).

Functional connectivity analysis

Functional connectivity analysis yielded significant differences between the LOT and EOT groups in the alpha 1, beta 3, and gamma frequency bands ($p < 0.05$). The LOT group demonstrated decreased lagged phase synchronization functional connectivity between the right primary auditory cortex (A1, BAs 41 and 42) and the

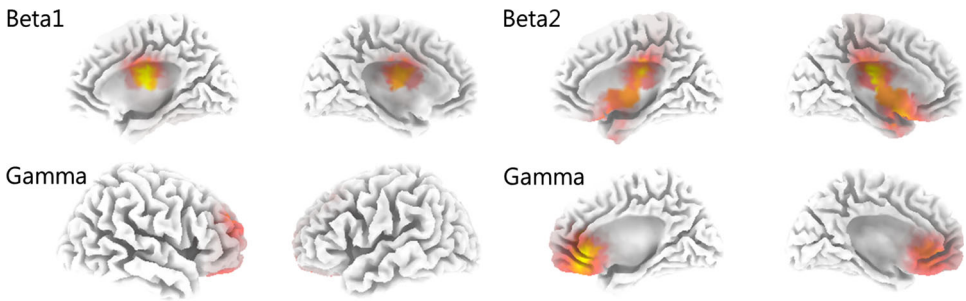

Fig. 1 sLORETA contrast analysis between the late-onset tinnitus (LOT) group and the early-onset tinnitus (EOT) group. Compared to the EOT group, the LOT group showed increased activities in the dorsal anterior cingulate cortex for beta 1, in the dorsal/subgenual anterior cingulate cortices and parahippocampus for the beta 2, and in the right pregenual anterior cingulate cortex and dorsolateral prefrontal cortex for the gamma frequency bands

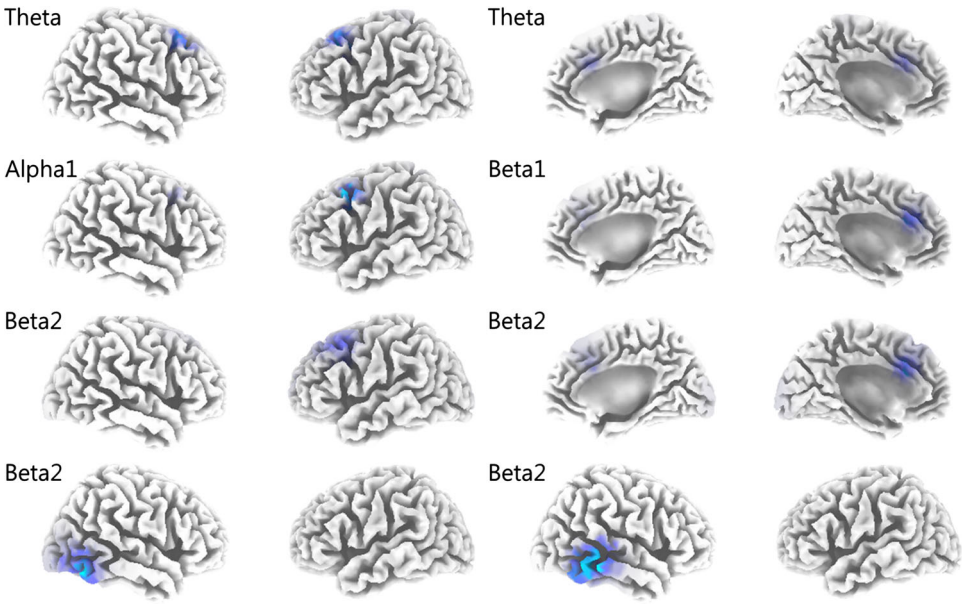

Fig. 2 sLORETA contrast analysis between old and young controls revealing overall decreased current densities in old controls. The decreased activity in old controls was most prominently shown in the dorsal anterior cingulate cortex for the theta, beta1/2 bands and in the bilateral dorsolateral prefrontal cortices for the theta, alpha1, and beta 2 frequency bands. Moreover, decreased beta3 activity in the right posterior inferior temporal gyrus and gamma activity in the right secondary auditory cortex were also observed in old controls when compared to young controls

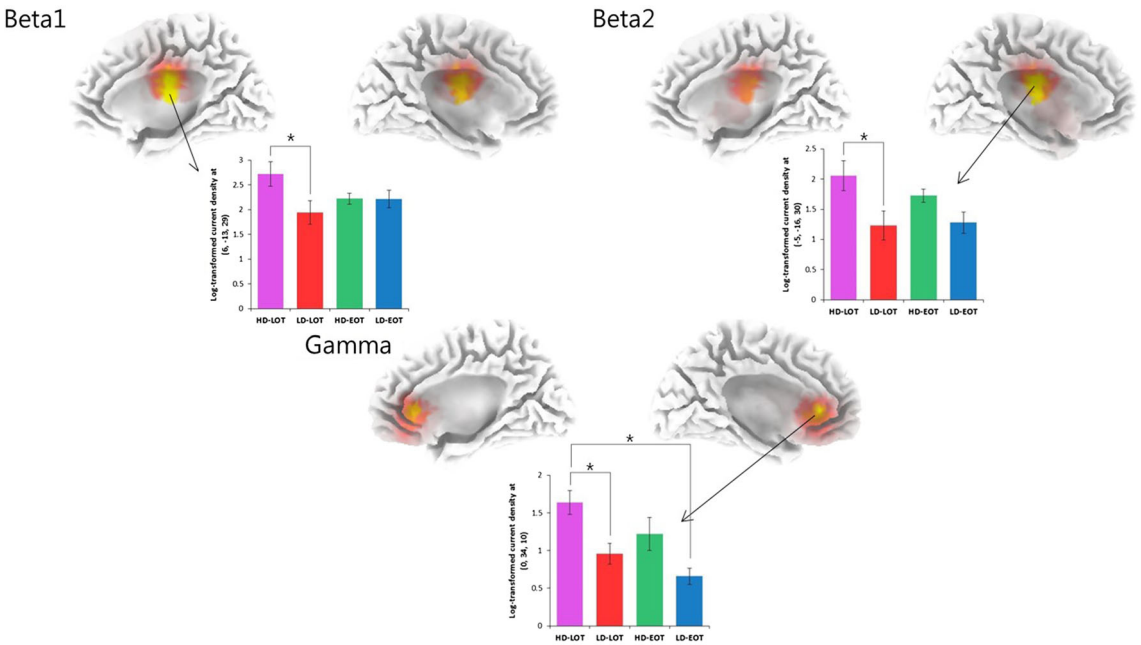

Fig. 3 sLORETA contrast analysis between the low distress (LD) and high distress (HD) subgroups of the LOT group. Compared to the LD–LOT subgroup, the HD–LOT subgroup demonstrated increased activities in the dorsal anterior cingulate cortex for beta 1 and 2, and pregenual anterior cingulate cortex for the gamma frequency bands. *Bar plots* depict the relative effect size among the four subgroups in those regions where the HD–LOT subgroup showed increased activity as compared with the LD–LOT subgroup

right posterior cingulate cortex (PCC)/precuneus (BAs 30 and 7, respectively) for the alpha 1 frequency band (Fig. 5a), and between the right A1 and left precuneus for the beta 3 frequency band, as compared with the EOT group (Fig. 5b). In contrast, the LOT group indicated significantly increased connectivity between the right sgACC and left A1, between the right medial temporal lobe and A1, and between the right PCC and precuneus for the gamma frequency band, as compared with the EOT group (Fig. 5c). Meanwhile, functional connectivity analyses between the HD–LOT and LD–LOT groups, as well as between the HD–EOT and LD–EOT groups, yielded no significant differences throughout the eight frequency bands.

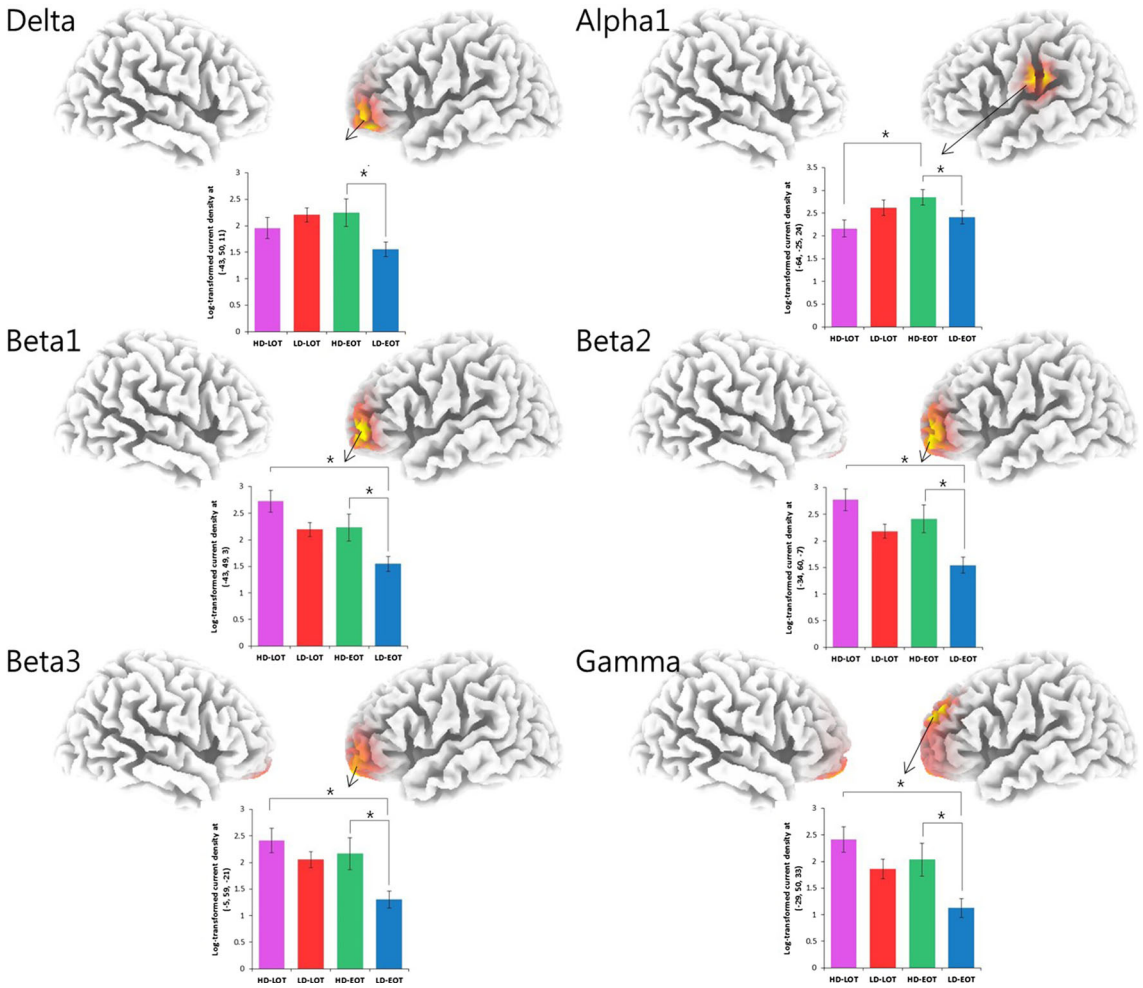

Fig. 4 sLORETA contrast analysis between the low distress (LD) and high distress (HD) subgroups of the EOT group. Compared to the LD–EOT subgroup, the HD–EOT subgroup showed increased activities in the left orbitofrontal cortex for the delta, beta 1/2/3, and gamma, and in the left supramarginal gyrus for the alpha 1, and in the left dorsolateral prefrontal cortex for the gamma frequency bands. *Bar plots* depict the relative effect size among the four subgroups in those regions where the HD–EOT subgroup showed increased activity as compared with the LD–EOT subgroup

Comparison of average current density among the 4 subgroups

For the areas found to be significantly more activated in the HD–LOT group than in the LD–LOT group, an ANOVA was performed. With the mean current density in the right dACC (6, −13, 29) beta 1 frequency band as a dependent variable, and with distress (HD vs. LD) and group (LOT vs. EOT) as independent variables, the main effect for distress (F (1,53) = 4.10, $p < .05$) and the interaction effect (distress x group) (F (1,53) = 4.39, $p < .05$) were significant, while the main effect for group (F (1,53) = .20, $p = .66$) was not significant (Fig. 6a). Likewise, ANOVA performed with the mean current density in the left dACC (−5, −16, 30) beta 2 frequency band revealed significant main effect for distress (F (1,53) = 9.68, $p < .05$), but the main effect for group (F (1,53) = .50, $p = .48$) and the interaction effect (distress × group) (F (1,53) = 0.89, $p = .35$) were not significant (Fig. 6b).

The same analyses were performed for the areas significantly more activated in the HD–EOT group than in the LD–EOT group. ANOVA of the left OFC (−43, 50, −11) delta frequency band as a dependent variable yielded significant interaction effect (distress x group) (F (1,53) = 3.86, $p < .05$) (Fig. 6c), but another ANOVA with the left OFC (−43, 49, 3) beta1 frequency showed non-significant interaction effect (F (1,53) = 0.84, $p = .37$) (Fig. 6d).

Predictability of tinnitus-related distress by local activities

The linear discriminant analysis for the LOT group using leave-one-out cross-validation showed that overall 78.6 %

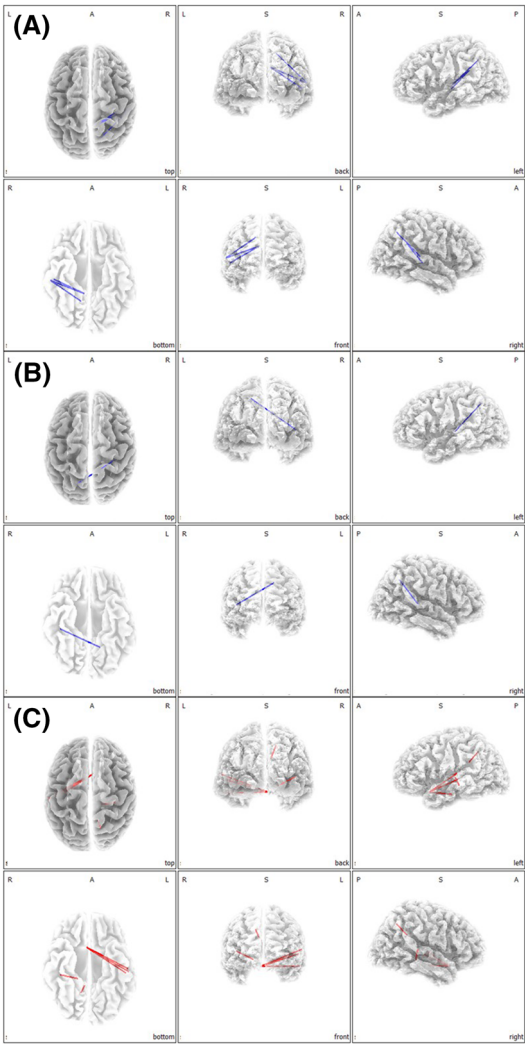

Fig. 5 Connectivity contrast analysis between the late-onset tinnitus (LOT) group and the early-onset tinnitus (EOT) group. The LOT group demonstrated decreased lagged phase synchronization functional connectivity between the right primary auditory cortex and the right posterior cingulate cortex/precuneus for the alpha 1 frequency band (**a**) and between the right primary auditory cortex and left precuneus for the beta 3 frequency band as compared with the EOT group (**b**). In contrast, the LOT group indicated significantly increased connectivity between the right subgenual anterior cingulate cortex and the left primary auditory cortex, between the right medial temporal lobe and primary auditory cortex, and between the right posterior cingulate cortex and precuneus for the gamma frequency band (**c**)

(22 of 28 LOT participants) were correctly classified to their subgroups, and the discriminant function revealed significant power of subgroup classification (Wilk's lambda = 0.662, $p < 0.05$). Using the same variables, the whole 4 subgroup-level analysis displayed that overall 47.4 % (27 of 57 participants) were correctly classified to their subgroups (Wilk's lambda = 0.598, $p < 0.05$).

Meanwhile, the discriminant function for the EOT group indicated trend-level significance (Wilk's lambda = 0.723, $p = 0.09$) and a correct subgroup classification rate of 72.4 % (21 of 29 EOT participants). In short, the activity in the dACC and pgACC significantly predicted high or low distress for the LOT group, with activity in the OFC and DLPFC showing non-significant predictability for the EOT group. Using the same variables, the whole 4 subgroup-level analysis displayed that overall 47.4 % (27 of 57 participants) were correctly classified to their subgroups (Wilk's lambda = 0.587, $p < 0.05$).

Discussion

This study demonstrates that tinnitus distress in elderly patients is generated by a different network than in younger patients, and that the differences cannot be explained by differences in mood and anxiety, hearing loss, perceived tinnitus loudness, tinnitus duration, or by a difference in the amount of distress.

Whereas tinnitus distress in a younger population is generated by neocortical areas, including the OFC, DLPFC and inferior parietal area, the distress in elderly patients is generated by the cingulate cortex,

It is of interest that those areas that differ (ACC, OFC and inferior parietal area), except for the DLPFC, are the only areas that show non-linear inverted U changes with age (Thambisetty et al. 2010) and that the left ACC increases in thickness with aging (Terribilli et al. 2011). Thus, the changes detected in current density might reflect structural changes, so that the decrease in volume in the DLPFC, OFC and inferior parietal area is structurally and functionally compensated for by the ACC.

As mentioned above, our recent study on the differences in brain activity between LOT and EOT revealed increased activity in areas previously described as being part of a tinnitus distress network such as the dACC, PFC, and insulae (Song et al. 2013a). From these results, we recognized that not only healthy aging brains, but also the brains of elderly tinnitus patients may be different from their younger counterparts.

Extending our previous work, we explored the applicability of our previous findings to other types of tinnitus. Specifically, we investigated bilateral pure-tone tinnitus participants whereas we only looked into bilateral NBN in our previous study on the differences between LOT and EOT. In replication of our previous study, the comparison between late- and early-onset participants with bilateral pure-tone tinnitus revealed significantly increased activity in the dACC for the beta1 band, increased dACC/sgACC and PHC activity for the beta2 band, and increased gamma frequency activity in the right pgACC, right OFC, and DLPFC (Fig. 1). Also, the LOT group indicated significantly increased connectivity between the right sgACC and

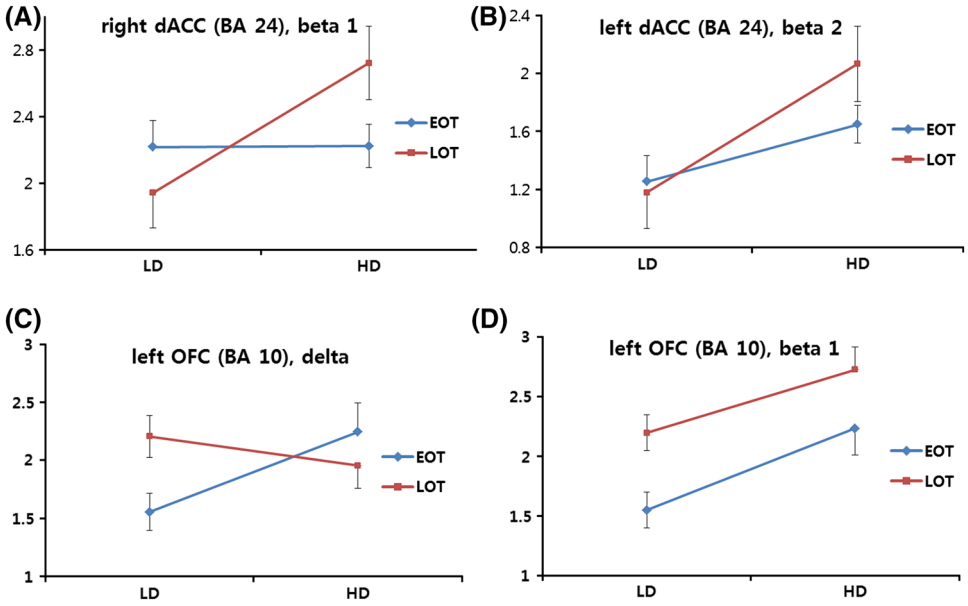

Fig. 6 Comparison of average current density among the 4 subgroups in the regions activated significantly in the HD–LOT subgroup as compared with the LD–LOT subgroup (**a**, **b**) and in the HD–EOT subgroup as compared with the LD–EOT subgroup (**c**, **d**)

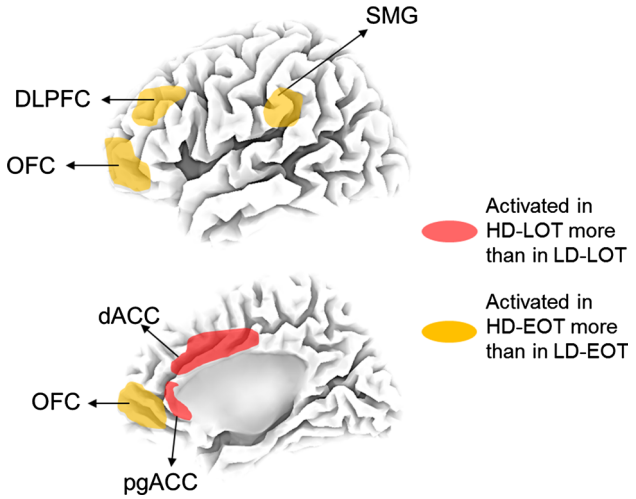

Fig. 7 Schematic summary of the areas with increased activities in the high distress late- and early-onset subgroups. *SMG* supramarginal gyrus, *DLPFC* dorsolateral prefrontal cortex, *OFC* orbitofrontal cortex, *dACC* dorsal anterior cingulate cortex, *pgACC* pregenual anterior cingulate cortex

left A1 (Fig. 6c). These results confirm our previous results in NBN tinnitus and we, therefore, generalize our finding of increased activity in the anterior cingulate and frontal areas in people with LOT as compared to those with EOT. In addition, by revealing overall decreased activities in the old control group as compared with the young control group, we confirmed that the differences in the LOT and EOT groups are not merely normal aging-related findings, but are purely tinnitus-related results. We also found some different regions of relative activation or deactivation between our previous study and the current study. These differences may be attributed to the intrinsic differences between NBN tinnitus and pure-tone tinnitus. Previous research has indicated that NBN tinnitus differs from pure-tone tinnitus in the lateral frontopolar area, PCC, and the PHC area (Vanneste et al. 2010c). Most of these regions were the areas where differences were found between our previous study (Song et al. 2013a) and the current study.

Our primary goal in the current study was to investigate the possible differences in neural substrates of tinnitus-related distress between the LOT and EOT groups. Since our recent work revealed that the LOT group activates a previously described tinnitus-related distress network, as compared with the EOT group, we further conjectured that LOT and EOT may also differ with regard to the neural substrates of tinnitus-related distress. Indeed, the HD–LOT group demonstrated increased activities in the dACC for the beta 1/2, and in the pgACC for the gamma frequency band, in comparison to the LD–LOT group, while the HD–EOT group indicated increased activities in the left OFC for the delta, beta 1/2/3, and gamma frequency bands, and in the left DLPFC for the gamma frequency band, as compared to the LD–EOT group (for summary, see Fig. 7). Also, by finding greater activity in the dACC for the beta 1 and 2 bands by the contrast "the HD–LOT group minus the HD–EOT group" and in the left OFC by the contrast "the LD–LOT group minus the LD–EOT group", we found interaction effects of the two independent variables, namely the onset age and the level of distress. Linear discrimination analysis further revealed that higher dACC and pgACC activities significantly predict higher distress level in the LOT group.

Recent studies have attempted to clarify neural substrates of tinnitus-related distress using various imaging modalities such as qEEG (Vanneste et al. 2010a), positron

emission tomography (Schecklmann et al. 2013), and functional magnetic resonance imaging (Golm et al. 2013). Although there are study-to-study disparities, probably due to different study paradigms, these studies reveal the ACC, insula, PHC, amygdala (Vanneste et al. 2010a), and the left middle frontal gyrus (Golm et al. 2013) as neural substrates of tinnitus-related distress. However, these studies included tinnitus participants with a mean age ranging from 49 to 53.9 years. In contrast, in the current study these mean ages are closer to the mean age of the LOT group than to those of the EOT group. Therefore, these studies may have been biased toward the relatively activated areas of the HD–LOT group. With regard to this, most of the areas of the alleged tinnitus-related distress networks may have been predominantly LOT-related distress networks.

The human brain volume decreases with age (Stark et al. 2007), and this is attributed to marked loss of glial cells and resultant loss of myelinated nerve fibers (Fabricius et al. 2013; Marner et al. 2003). Especially, the ACC, the proposed interface between emotion and cognition (Lane et al. 1998), has been reported to show significant normal aging-related volume declines, as measured by voxel-based morphometry (Mann et al. 2011), and decreased activations as measured by fMRI or PET (Pardo et al. 2007; Taki et al. 2012). However, it has also been shown that the ACC is uniquely activated in patients with late-onset refractory depression, as compared with normal old controls (Marano et al. 2013) or non-refractory patients (Awata et al. 1998). In addition, late-onset anxious depression patients showed significantly greater and more sustained activation in the dACC than late-onset depression patients with less anxiety (Andreescu et al. 2009). Moreover, elderly depression patients with high and low comorbid anxiety showed different connectivity patterns of the ACC and PCC (Andreescu et al. 2011). Considering the similarities between the abovementioned late-onset depression with high and low anxiety groups, and our HD–LOT and LD–LOT groups, respectively, we may regard the relatively increased activity in the dACC and pgACC as a more general signature of high distress in the context of late-onset pathologies of similar characteristics.

The OFC has been implicated in many psychiatric disorders including depression, anxiety, phobia, and obsessive–compulsive disorder (Bachevalier et al. 2011). Previous research has also shown that the OFC is important for emotional processing of sounds (Dias et al. 1996; Blood et al. 1999). For example, patients with OFC lesions had reduced self-evaluated perception of the unpleasantness of the acoustic probe stimulus (Angrilli et al. 2008). In this context, increased activity in the OFC of the HD–EOT group may indicate that young tinnitus subjects with high distress suffer from unpleasant emotional processing of tinnitus sound. Other studies have demonstrated that the OFC is part of the reward system (Rolls 2004; Kringelbach 2005), so it is possible that people with HD–EOT are distressed due to increased activity in the OFC that integrates aversive information from perceived tinnitus.

The differences in neural substrates of tinnitus-related distress between the LOT and EOT groups in the current study may be of importance from a therapeutic point of view. For instance, recent literature has indicated that transcranial magnetic stimulation (TMS) can modulate tinnitus-related distress (Lee et al. 2013). Notably, TMS by a double cone coil can modulate the ACC (Vanneste and De Ridder 2012), and DLPFC stimulation by TMS, transcranial direct current stimulation, or electrode implant can improve tinnitus intensity (De Ridder et al. 2012; De Ridder et al. 2013) and tinnitus-related distress (Vanneste et al. 2010b). Based on the results of the current study, we hypothesize that TMS targeting the dACC/pgACC may yield better results in patients with LOT than those with EOT. In contrast, neurostimulation targeting the OFC or the DLPFC may be of more benefit to patients with EOT than to those with LOT. In this regard, future studies exploring treatment response according to the age of tinnitus onset may be of additional value.

From a pathophysiologic point of view, the results of the current study may be applicable to various future studies on similar pathologies. As pathologies such as pain, post-traumatic stress disorder, or depressive disorder show similarities to tinnitus, we speculate that these disease entities may similarly reveal different neural substrates of distress according to the age of onset. This, in turn, could be valuable in constructing calibrated strategies for treatment. We see the current study as a pioneer work along these lines.

Limitation of the study has to be mentioned. The LOT and EOT groups differ not only in the age of onset, but also in the current age. Therefore, to see if the results of the current study are due to either the age of onset or the current age, future longitudinal study in which different onset-age groups are followed up should be performed.

Taken together, we found that late-onset tinnitus participants with high distress showed reduced activity in the dACC and pgACC relative to those with low distress, while early-onset tinnitus participants with high distress showed more activity in the OFC and DLPFC relative to those with low distress. These findings may prove to be valuable for planning individualized treatment regiments calibrated to the age of tinnitus onset and for understanding differences in the origin of distress between the early and late onset of similar pathologies.

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References

Andreescu C, Butters M, Lenze EJ, Venkatraman VK, Nable M, Reynolds CF 3rd, Aizenstein HJ (2009) fMRI activation in late-life anxious depression: a potential biomarker. Int J Geriatr Psychiatry 24:820–828

Andreescu C, Wu M, Butters MA, Figurski J, Reynolds CF 3rd, Aizenstein HJ (2011) The default mode network in late-life anxious depression. Am J Geriatr Psychiatry 19:980–983

Angrilli A, Bianchin M, Radaelli S, Bertagnoni G, Pertile M (2008) Reduced startle reflex and aversive noise perception in patients with orbitofrontal cortex lesions. Neuropsychologia 46:1179–1184

Awata S, Ito H, Konno M, Ono S, Kawashima R, Fukuda H, Sato M (1998) Regional cerebral blood flow abnormalities in late-life depression: relation to refractoriness and chronification. Psychiatry Clin Neurosci 52:97–105

Axelsson A, Ringdahl A (1989) Tinnitus—a study of its prevalence and characteristics. Br J Audiol 23:53–62

Bachevalier J, Machado CJ, Kazama A (2011) Behavioral outcomes of late-onset or early-onset orbital frontal cortex (areas 11/13) lesions in rhesus monkeys. Ann N Y Acad Sci 1239:71–86

Bjelland I, Dahl AA, Haug TT, Neckelmann D (2002) The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res 52:69–77

Blood AJ, Zatorre RJ, Bermudez P, Evans AC (1999) Emotional responses to pleasant and unpleasant music correlate with activity in paralimbic brain regions. Nat Neurosci 2:382–387

Bruder GE, Bansal R, Tenke CE, Liu J, Hao X, Warner V, Peterson BS, Weissman MM (2012) Relationship of resting EEG with anatomical MRI measures in individuals at high and low risk for depression. Hum Brain Mapp 33:1325–1333

Damasio AR (1996) The somatic marker hypothesis and the possible functions of the prefrontal cortex. Philos Trans R Soc Lond B Biol Sci 351:1413–1420

Davis SW, Dennis NA, Daselaar SM, Fleck MS, Cabeza R (2008) Que PASA? The posterior-anterior shift in aging. Cereb Cortex 18:1201–1209

De Ridder D, Elgoyhen AB, Romo R, Langguth B (2011) Phantom percepts: tinnitus and pain as persisting aversive memory networks. Proc Natl Acad Sci USA 108:8075–8080

De Ridder D, Vanneste S, Plazier M, Menovsky T, van de Heyning P, Kovacs S, Sunaert S (2012) Dorsolateral prefrontal cortex transcranial magnetic stimulation and electrode implant for intractable tinnitus. World Neurosurg 77:778–784

De Ridder D, Song JJ, Vanneste S (2013) Frontal cortex TMS for tinnitus. Brain Stimul 6:355–362

Dias R, Robbins TW, Roberts AC (1996) Dissociation in prefrontal cortex of affective and attentional shifts. Nature 380:69–72

Dierks T, Jelic V, Pascual-Marqui RD, Wahlund L, Julin P, Linden DE, Maurer K, Winblad B, Nordberg A (2000) Spatial pattern of cerebral glucose metabolism (PET) correlates with localization of intracerebral EEG-generators in Alzheimer's disease. Clin Neurophysiol 111:1817–1824

Fabricius K, Jacobsen JS, Pakkenberg B (2013) Effect of age on neocortical brain cells in 90+ year old human females—a cell counting study. Neurobiol Aging 34:91–99

Farrior JB (1956) Fenestration operation in the poor candidates; 44 cases selected from 637 operations. Laryngoscope 66:566–573

Fuchs M, Kastner J, Wagner M, Hawes S, Ebersole JS (2002) A standardized boundary element method volume conductor model. Clin Neurophysiol 113:702–712

Gates GA, Cooper JC (1991) Incidence of hearing decline in the elderly. Acta Otolaryngol 111:240–248

Goebel G, Hiller W (1994) The tinnitus questionnaire. A standard instrument for grading the degree of tinnitus. Results of a multicenter study with the tinnitus questionnaire. HNO 42:166–172

Golm D, Schmidt-Samoa C, Dechent P, Kroner-Herwig B (2013) Neural correlates of tinnitus related distress: an fMRI-study. Hear Res 295:87–99

Holmes AP, Blair RC, Watson JD, Ford I (1996) Nonparametric analysis of statistic images from functional mapping experiments. J Cereb Blood Flow Metab 16:7–22

Hwang JH, Chou PH, Wu CW, Chen JH, Liu TC (2009) Brain activation in patients with idiopathic hyperacusis. Am J Otolaryngol 30:432–434

Jastreboff PJ (1990) Phantom auditory perception (tinnitus): mechanisms of generation and perception. Neurosci Res 8:221–254

Jurcak V, Tsuzuki D, Dan I (2007) 10/20, 10/10, and 10/5 systems revisited: their validity as relative head-surface-based positioning systems. Neuroimage 34:1600–1611

Khedr EM, Ahmed MA, Shawky OA, Mohamed ES, El Attar GS, Mohammad KA (2010) Epidemiological study of chronic tinnitus in Assiut, Egypt. Neuroepidemiology 35:45–52

Kringelbach ML (2005) The human orbitofrontal cortex: linking reward to hedonic experience. Nat Rev Neurosci 6:691–702

Lane RD, Reiman EM, Axelrod B, Yun LS, Holmes A, Schwartz GE (1998) Neural correlates of levels of emotional awareness. Evidence of an interaction between emotion and attention in the anterior cingulate cortex. J Cogn Neurosci 10:525–535

Lee HY, Yoo SD, Ryu EW, Byun JY, Yeo SG, Park MS (2013) Short term effects of repetitive transcranial magnetic stimulation in patients with catastrophic intractable tinnitus: preliminary report. Clin Exp Otorhinolaryngol 6:63–67

Levitin DJ, Menon V, Schmitt JE, Eliez S, White CD, Glover GH, Kadis J, Korenberg JR, Bellugi U, Reiss AL (2003) Neural correlates of auditory perception in Williams syndrome: an fMRI study. Neuroimage 18:74–82

Logan JM, Sanders AL, Snyder AZ, Morris JC, Buckner RL (2002) Under-recruitment and nonselective recruitment: dissociable neural mechanisms associated with aging. Neuron 33:827–840

Mahoney CJ, Rohrer JD, Goll JC, Fox NC, Rossor MN, Warren JD (2011) Structural neuroanatomy of tinnitus and hyperacusis in semantic dementia. J Neurol Neurosurg Psychiatry 82:1274–1278

Mann SL, Hazlett EA, Byne W, Hof PR, Buchsbaum MS, Cohen BH, Goldstein KE, Haznedar MM, Mitsis EM, Siever LJ, Chu KW (2011) Anterior and posterior cingulate cortex volume in healthy adults: effects of aging and gender differences. Brain Res 1401:18–29

Marano CM, Workman CI, Kramer E, Hermann CR, Ma Y, Dhawan V, Chaly T, Eidelberg D, Smith GS (2013) Longitudinal studies of cerebral glucose metabolism in late-life depression and normal aging. Int J Geriatr Psychiatry 28:417–423

Marner L, Nyengaard JR, Tang Y, Pakkenberg B (2003) Marked loss of myelinated nerve fibers in the human brain with age. J Comp Neurol 462:144–152

Meeus O, Blaivie C, Van de Heyning P (2007) Validation of the Dutch and the French version of the Tinnitus Questionnaire. B-ENT 3(Suppl 7):11–17

Meeus O, Heyndrickx K, Lambrechts P, De Ridder D, Van de Heyning P (2010) Phase-shift treatment for tinnitus of cochlear origin. Eur Arch Otorhinolaryngol 267:881–888

Mirandola P, Gobbi G, Malinverno C, Carubbi C, Ferne FM, Artico M, Vitale M, Vaccarezza M (2013) Impact of sulphurous water politzer inhalation on audiometric parameters in children with otitis media with effusion. Clin Exp Otorhinolaryngol 6:7–11

Moazami-Goudarzi M, Michels L, Weisz N, Jeanmonod D (2010) Temporo-insular enhancement of EEG low and high frequencies in patients with chronic tinnitus. QEEG study of chronic tinnitus patients. BMC Neurosci 11:40

Mulert C, Jager L, Schmitt R, Bussfeld P, Pogarell O, Moller HJ, Juckel G, Hegerl U (2004) Integration of fMRI and simultaneous EEG: towards a comprehensive understanding of localization and time-course of brain activity in target detection. Neuroimage 22:83–94

Nichols TE, Holmes AP (2002) Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum Brain Mapp 15:1–25

Nondahl DM, Cruickshanks KJ, Huang GH, Klein BE, Klein R, Tweed TS, Zhan W (2012) Generational differences in the reporting of tinnitus. Ear Hear 33:640–644

Pardo JV, Lee JT, Sheikh SA, Surerus-Johnson C, Shah H, Munch KR, Carlis JV, Lewis SM, Kuskowski MA, Dysken MW (2007) Where the brain grows old: decline in anterior cingulate and medial prefrontal function with normal aging. Neuroimage 35:1231–1237

Pascual-Marqui RD (2002) Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. Methods Find Exp Clin Pharmacol 24 Suppl D:5–12

Pascual-Marqui RD (2007) Instantaneous and lagged measurements of linear and nonlinear dependence between groups of multivariate time series: frequency decomposition. Arxiv preprint arXiv:07111455

Pizzagalli D, Pascual-Marqui RD, Nitschke JB, Oakes TR, Larson CL, Abercrombie HC, Schaefer SM, Koger JV, Benca RM, Davidson RJ (2001) Anterior cingulate activity as a predictor of degree of treatment response in major depression: evidence from brain electrical tomography analysis. Am J Psychiatry 158:405–415

Pizzagalli DA, Oakes TR, Fox AS, Chung MK, Larson CL, Abercrombie HC, Schaefer SM, Benca RM, Davidson RJ (2004) Functional but not structural subgenual prefrontal cortex abnormalities in melancholia. Mol Psychiatry 9(325):393–405

Rolls ET (2004) The functions of the orbitofrontal cortex. Brain Cogn 55:11–29

Schecklmann M, Landgrebe M, Poeppl TB, Kreuzer P, Manner P, Marienhagen J, Wack DS, Kleinjung T, Hajak G, Langguth B (2013) Neural correlates of tinnitus duration and distress: a positron emission tomography study. Hum Brain Mapp 34:233–240

Schlee W, Kleinjung T, Hiller W, Goebel G, Kolassa IT, Langguth B (2011) Does tinnitus distress depend on age of onset? PLoS ONE 6:e27379

Segrave RA, Cooper NR, Thomson RH, Croft RJ, Sheppard DM, Fitzgerald PB (2011) Individualized alpha activity and frontal asymmetry in major depression. Clin EEG Neurosci 42:45–52

Shargorodsky J, Curhan GC, Farwell WR (2010) Prevalence and characteristics of tinnitus among US adults. Am J Med 123:711–718

Sherlin L, Congedo M (2005) Obsessive-compulsive dimension localized using low-resolution brain electromagnetic tomography (LORETA). Neurosci Lett 387:72–74

Song JJ, Choi HG, Oh SH, Chang SO, Kim CS, Lee JH (2009) Unilateral sensorineural hearing loss in children: the importance of temporal bone computed tomography and audiometric follow-up. Otol Neurotol 30:604–608

Song JJ, De Ridder D, Van de Heyning P, Vanneste S (2012a) Mapping tinnitus-related brain activation: an activation-likelihood estimation metaanalysis of PET studies. J Nucl Med 53:1550–1557

Song JJ, Hong SK, Kim JS, Koo JW (2012b) Enlarged vestibular aqueduct may precipitate benign paroxysmal positional vertigo in children. Acta Otolaryngol 132(Suppl 1):S109–S117

Song JJ, De Ridder D, Schlee W, Van de Heyning P, Vanneste S (2013a) "Distressed aging": the differences in brain activity between early- and late-onset tinnitus. Neurobiol Aging 34:1853–1863

Song JJ, Punte AK, De Ridder D, Vanneste S, Van de Heyning P (2013b) Neural substrates predicting improvement of tinnitus after cochlear implantation in patients with single-sided deafness. Hear Res 299:1–9

Song JJ, De Ridder D, Weisz N, Schlee W, Van de Heyning P, Vanneste S (2013b) Hyperacusis-associated pathological resting-state brain oscillations in the tinnitus brain: a hyperresponsiveness network with paradoxically inactive auditory cortex. Brain Struct Funct

Stark AK, Toft MH, Pakkenberg H, Fabricius K, Eriksen N, Pelvig DP, Moller M, Pakkenberg B (2007) The effect of age and gender on the volume and size distribution of neocortical neurons. Neuroscience 150:121–130

Taki Y, Thyreau B, Kinomura S, Sato K, Goto R, Wu K, Kawashima R, Fukuda H (2012) A longitudinal study of age- and gender-related annual rate of volume changes in regional gray matter in healthy adults. Hum Brain Mapp

Terribilli D, Schaufelberger MS, Duran FL, Zanetti MV, Curiati PK, Menezes PR, Scazufca M, Amaro E Jr, Leite CC, Busatto GF (2011) Age-related gray matter volume changes in the brain during non-elderly adulthood. Neurobiol Aging 32:354–368

Thambisetty M, Wan J, Carass A, An Y, Prince JL, Resnick SM (2010) Longitudinal changes in cortical thickness associated with normal aging. Neuroimage 52:1215–1223

Vanneste S, De Ridder D (2012) The use of alcohol as a moderator for tinnitus-related distress. Brain Topogr 25:97–105

Vanneste S, Plazier M, der Loo E, de Heyning PV, Congedo M, De Ridder D (2010a) The neural correlates of tinnitus-related distress. Neuroimage 52:470–480

Vanneste S, Plazier M, Ost J, van der Loo E, Van de Heyning P, De Ridder D (2010b) Bilateral dorsolateral prefrontal cortex modulation for tinnitus by transcranial direct current stimulation: a preliminary clinical study. Exp Brain Res 202:779–785

Vanneste S, Plazier M, van der Loo E, Van de Heyning P, De Ridder D (2010c) The differences in brain activity between narrow band noise and pure tone tinnitus. PLoS ONE 5:e13618

Varela F, Lachaux JP, Rodriguez E, Martinerie J (2001) The brainweb: phase synchronization and large-scale integration. Nat Rev Neurosci 2:229–239

Vitacco D, Brandeis D, Pascual-Marqui R, Martin E (2002) Correspondence of event-related potential tomography and functional magnetic resonance imaging during language processing. Hum Brain Mapp 17:4–12

Volkow ND, Logan J, Fowler JS, Wang GJ, Gur RC, Wong C, Felder C, Gatley SJ, Ding YS, Hitzemann R, Pappas N (2000) Association between age-related decline in brain dopamine activity and impairment in frontal and cingulate metabolism. Am J Psychiatry 157:75–80

Volpe U, Mucci A, Bucci P, Merlotti E, Galderisi S, Maj M (2007) The cortical generators of P3a and P3b: a LORETA study. Brain Res Bull 73:220–230

Volz KG, von Cramon DY (2009) How the orbitofrontal cortex contributes to decision making—a view from neuroscience. Prog Brain Res 174:61–71

Worrell GA, Lagerlund TD, Sharbrough FW, Brinkmann BH, Busacker NE, Cicora KM, O'Brien TJ (2000) Localization of the epileptic focus by low-resolution electromagnetic

tomography in patients with a lesion demonstrated by MRI. Brain Topogr 12:273–282

Zumsteg D, Wennberg RA, Treyer V, Buck A, Wieser HG (2005) H2(15)O or 13NH3 PET and electromagnetic tomography (LORETA) during partial status epilepticus. Neurology 65:1657–1660

Zumsteg D, Lozano AM, Wennberg RA (2006a) Depth electrode recorded cerebral responses with deep brain stimulation of the anterior thalamus for epilepsy. Clin Neurophysiol 117:1602–1609

Zumsteg D, Lozano AM, Wennberg RA (2006b) Mesial temporal inhibition in a patient with deep brain stimulation of the anterior thalamus for epilepsy. Epilepsia 47:1958–1962

Zumsteg D, Lozano AM, Wieser HG, Wennberg RA (2006c) Cortical activation with deep brain stimulation of the anterior thalamus for epilepsy. Clin Neurophysiol 117:192–207