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ORIGINAL ARTICLE

Hyperacusis-associated pathological resting-state brain oscillations in the tinnitus brain: a hyperresponsiveness network with paradoxically inactive auditory cortex

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Abstract Although hyperacusis, a hyperresponsiveness to non-noxious auditory stimuli, is a sound-evoked symptom, possible resting-state pathologic oscillations in hyperacusis brain have never been explored. By comparing 17 tinnitus participants with hyperacusis (T+H+) and 17 without hyperacusis (T+H−), we aimed to explore characteristic resting-state cortical activity of hyperacusis. The T+H+ and T+H− groups, strictly matched for all tinnitus sound characteristics to exclude tinnitus-related cortical changes, were compared using resting-state electroencephalography source-localized activity complemented by functional connectivity analyses. Correlation analysis revealed that hyperacusis questionnaire score was positively correlated with the orbitofrontal cortex (OFC) beta power, the right auditory cortex (AC) alpha1 power, and the dorsal anterior cingulate cortex (dACC) beta1 power. Compared to the T+H− group, the T+H+ group demonstrated increased beta power in the dACC and OFC, and increased alpha power in the right AC. Region of interest analyses including 17 normal controls further confirmed that these differences originated solely from relatively increased power of the T+H+ group, not from a relative power decrease of the T+H− group. Also, the T+H+ group showed increased connectivity between the OFC/dACC and the AC as compared to the T+H− group. The beta power increase in the OFC/dACC may indicate increased resting-state vigilance in tinnitus patients with hyperacusis. In addition, increased alpha power in the AC may reflect an adaptive top-down inhibition against sound stimuli probably mediated by the increased beta power of the OFC. The OFC/dACC, also frequently found to be activated in analogous diseases such as allodynia/hyperalgesia, may compose a hyperresponsiveness network.

Keywords Hyperacusis · Hyperalgesia · Electroencephalography · Neural networks

Abbreviations

HQ	Hyperacusis questionnaire
qEEG	Quantitative electroencephalography

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TQ	Tinnitus questionnaire
NRS	Numeric rating scale
sLORETA	Standardized low-resolution brain electromagnetic tomography
MNI	Montreal Neurological Institute
ROI	Region of interest
AC	Auditory cortex
A2	Secondary auditory cortex
A1	Primary auditory cortex
dACC	Dorsal anterior cingulate cortex
OFC	Orbitofrontal cortex
SnPM	Statistical non-parametric mapping
SMA	Supplementary motor area
dPMC	Dorsal premotor cortex

Introduction

Hyperacusis has been defined as "an unusual intolerance to ordinary environmental sounds" (Vernon 1987) or as "physical discomfort resulting from an exposure to moderate or even weak sound that would not evoke a similar reaction in an average person" (Hiller and Goebel 2006). Although there are minute differences in description, these definitions are generally based on the idea that hyperacusic patients cannot tolerate sounds or sound levels acceptable for the general population.

The reported prevalence of hyperacusis ranges from 8 to 15.2 % (Andersson et al. 2002; Baguley 2003), but may have been underestimated because it is frequently overlooked when it occurs in combination with other medical conditions (Marriage and Barnes 1995). Indeed, hyperacusis is often reported as a symptom in various neurological diseases, including Williams syndrome, migraine, meningitis, traumatic head injury, Ramsey-Hunt syndrome, Lyme disease, and tinnitus (Gothelf et al. 2006; Woodhouse and Drummond 1993; Dauman and Bouscau-Faure 2005; Moller 2007b). Of these, tinnitus is one of the most common diseases that accompany hyperacusis. The reported prevalence for sound intolerance in tinnitus patients ranges widely, probably due to various definitions and questionnaires for hyperacusis, from 30 up to 79 % (Dauman and Bouscau-Faure 2005; Meeus et al. 2010b). Moreover, 88 % of the patients whose chief complaint was hyperacusis also reported tinnitus (Anari et al. 1999). A recent animal study has also asserted that high doses of salicylate, a reliable inducer of tinnitus, can also cause a significant enhancement of sound-evoked cortical response and acoustic startle response mimicking hyperacusis (Sun et al. 2008).

Pathophysiological mechanisms of hyperacusis have been suggested, e.g., disruptions in the amplification and regulation processes of the cochlear outer hair cells or of central auditory system gain for sound stimulation (Katzenell and Segal 2001; Herraiz et al. 2006). Interestingly similar mechanisms have also frequently been associated with central neuropathic patients suffering painful sensations from innocuous somatosensory stimulation (allodynia) or abnormally increased sensation of pain or discomfort produced by minimally noxious stimuli (hyperpathia/hyperalgesia). The similarities of the symptom (i.e., exaggerated reaction to sensory stimuli) as well as pathogenesis level between hyperacusis and neuropathic pain have already been noted by previous authors (Moller2006, 2007a; De Ridder et al. 2011) and have been subsumed under the term "plasticity diseases" (Moller 2009) expressing the conceptual assumption that harmful neural plasticity leads to the hyperactivation in hyperacusis and allodynia/hyperalgesia.

However, empirical evidence for this assumption has not been reported yet and the underlying mechanism of hyperacusis is currently unknown. Previous animal research demonstrated enhanced responsiveness of the auditory cortex (AC) by showing increased sound-evoked potentials and spike firing rates as well as exaggerated acoustic startle response, a behavioral correlate of hyperacusis, after salicylate injection (Norena et al. 2010; Sun et al. 2009; Turner and Parrish 2008) or noise overexposure (Norena et al. 2010; Sun et al. 2012). However, these animal studies have limitations in that most studies investigated hyperacusis as a by-product while focusing at tinnitus, and cortical activities other than the AC were not evaluated. Meanwhile, as an approach to reveal the neural correlates of hyperacusis, functional imaging studies in humans have been performed in idiopathic hyperacusis participants (Hwang et al. 2009) and hyperacusis participants with other diseases such as Williams syndrome (Levitin et al. 2003) or semantic dementia (Mahoney et al. 2011). Notwithstanding these efforts, the knowledge of the neural correlates of hyperacusis is still limited due to restricted number of study participants and possible biasing effect of combined diseases to the results.

One of the biggest obstacles to unravel the neural correlates of hyperacusis is that participants whose presenting complaint is purely hyperacusis are extremely rare. Therefore, participants with the above-mentioned pathologies which are frequently associated with hyperacusis have been adopted to investigate hyperacusis-related neural correlates (Levitin et al. 2003; Mahoney et al. 2011). To obtain unbiased results by studying such participants, it is essential to conduct a study in a relatively large group that is well controlled for other factors affecting cortical activity. Using our large database of tinnitus patients, we found a relatively large amount of tinnitus participants with hyperacusis defined by hyperacusis questionnaire (HQ) (Khalfa et al. 2002) score. By strictly matching to the

tinnitus with hyperacusis group (T+H+ group) for all hitherto-described affecting factors of tinnitus and its related distress, we were able to obtain a control group of tinnitus participants without hyperacusis (T+H− group). By comparing these two groups, we attempted to retrospectively extract neural correlates only related to hyperacusis in tinnitus patients. In addition, we compared our findings with previous neuroimaging studies on allodynia/hyperalgesia to find commonalities and discrepancies and thus to find a common network associated with sensory hyperresponsiveness. Hereinafter, we describe the estimated neural correlates of hyperacusis analyzed by source-localized quantitative electroencephalography (qEEG).

Materials and methods

Participants

To maintain a homogenous study group, we selected a total of 235 participants with bilateral pure tone (PT) tinnitus from the database of the multidisciplinary Tinnitus Research Initiative Clinic of the University Hospital of Antwerp, Belgium. Of them, 63 participants have already completed a validated Dutch version (Meeus et al. 2007) of the hyperacusis questionnaire (HQ) (Khalfa et al. 2002) that comprises 14 self-rating items with a total score range of 0–42. From this group, participants scoring more than 28 on the HQ were allocated to the T+H+ group, as the score 28 has been suggested as the cut-off value for hyperacusis (Khalfa et al. 2002; Meeus et al. 2010b). Individuals with combined pulsatile tinnitus component, otologic disorders such as Ménière's disease or otosclerosis, conductive/sensorineural hearing loss exceeding the range of serviceable hearing threshold (40 dB) (Farrior 1956) in at least one ear, psychiatric or neurological disorder, chronic headache, drug/alcohol abuse, current psychotropic/central nervous system-active medications, and history of head injury (with loss of consciousness) or seizures were not included in the study. In this way, 17 of 235 participants with bilateral PT tinnitus and hyperacusis (15 males and 2 females) with a mean age of 41.0 ± 15.3 years (range 19–66) were included in the T+H+ group.

Meanwhile, from the rest 46 bilateral PT tinnitus participants scoring less than 28 on the HQ, 17 participants (14 males and 3 females) with a mean age of 40.8 ± 14.5 (range 21–66) were selected using one-by-one matching to the T+H+ participants with regard to all tinnitus sound characteristics while blinded to the raw EEG data and allocated to the T+H− group. As both the T+H+ and T+H− groups were selected from participants with bilateral PT tinnitus, possible differences in cortical activity arising from tinnitus sound characteristics (Vanneste et al. 2010b) and laterality (Vanneste et al. 2011a) could be minimized from the initial stage of participant selection. In addition, by selecting each T+H− patient who best matched to each T+H+ patient with regard to all possible affecting factors to the cortical activity of tinnitus brain (Song et al. 2012a) such as sex (Vanneste et al. 2012), age of tinnitus onset (Schlee et al. 2011; Vanneste et al. 2011b; Song et al. 2013a) duration of tinnitus (Schlee et al. 2009), and tinnitus questionnaire (TQ) (Hiller et al. 1994) score (Schecklmann et al. 2013; Vanneste et al. 2010a; Golm et al. 2013), we tried to compose near-ideal study groups for comparison. Also, to minimize selection bias with regards to the EEG findings, the authors were blinded to the raw EEG data of the patients while selecting the study groups. As a result, the T+H+ and T+H− groups showed no significant differences for sex, onset age and duration of tinnitus, Numeric Rating Scale (NRS) intensity (answering to a question "how loud is your tinnitus?" on a scale from 0 to 10), NRS distress (answering to a question "how bothered are you by your tinnitus?" On a scale from 0 to 10), and mean total TQ score (Table 1). Therefore, the two groups were maximally matched except for mean HQ score ($P < 0.001$). All participants underwent audiometry to measure hearing threshold and tinnitus matching to evaluate tinnitus frequency and intensity. Psychophysical tinnitus loudness and frequency matching were performed contralateral to the worse tinnitus ear as all the participants were bilateral PT tinnitus patients (Meeus et al. 2010a). No significant differences were found for hearing threshold between the two groups, as measured by a conventional hearing threshold calculation method (mean value of

Table 1 Participants' characteristics

	Tinnitus with hyperacusis group ($n = 17$)	Tinnitus without hyperacusis group ($n = 17$)	P values
Age (years)	41.0 ± 15.3	40.8 ± 14.5	0.97
Age of onset (years)	34.2 ± 16.5	32.3 ± 19.5	0.76
Male:female	15:2	14:3	–
Tinnitus duration (years)	4.3 ± 3.6	4.0 ± 5.9	0.87
Total score on tinnitus questionnaire	56.4 ± 14.4	51.5 ± 5.9	0.21
Hearing threshold (dB HL)	17.8 ± 5.1	17.2 ± 7.4	0.63
Hearing threshold at tinnitus frequency (dB HL)	35.3 ± 27.8	29.6 ± 26.6	0.55
Numeric rating scale intensity	7.2 ± 2.1	6.8 ± 1.8	0.52
Numeric rating scale distress	8.1 ± 1.7	7.6 ± 2.0	0.40
Total score on hyperacusis questionnaire	33.1 ± 3.6	17.8 ± 7.7	<0.001

hearing thresholds at 0.5, 1, and 2 kHz) (Song et al. 2009, 2012b; Mirandola et al. 2013) and the loss in decibels (dB HL) at the tinnitus frequency (Table 1). Therefore, possible cortical activity differences between the two groups due to different hearing level could be minimized.

EEG recording

This study has been approved by the Antwerp University Hospital Institutional Review Board ('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.

EEGs were recorded for approximately 5 min at 19 scalp sites using a Tin-electrode cap (ElectroCap, Ohio, United States), Mitsar amplifier (Mitsar EEG-201, St. Petersburg, Russia), and the WinEEG software version 2.84.44 (Mitsar, St. Pertersburg, Russia; available at: http://www.mitsar-medical.com) in a fully lighted room shielded against sound and stray electric fields with each participant eye-closed and sitting upright on a comfortable chair. The EEG was sampled with 19 electrodes in the standard 10–20 International placement referenced to linked ears, and impedances were maintained below 5 kΩ at all electrodes throughout the EEG recording. Data were recorded with a sampling rate of 1,024 Hz, a high-pass filter of 0.15 Hz, and a low-pass filter of 200 Hz. The off-line data processing involved resampling to 128 Hz and band-pass filtering (fast Fourier transform filter applying a Hanning window) with 2-44 Hz before the data were imported into the Eureka! Software (Sherlin and Congedo 2005). A careful inspection of artifacts was done manually and all episodic artifacts including eye blinks, eye movements, teeth clenching, or body movement were removed from the EEG stream. Also, further muscle artifacts were removed by independent component analysis (ICA) using ICoN software (http://sites.google.com/site/marcocongedo/software/nica) (Koprivova et al. 2011; White et al. 2012).

Participants abstained from alcohol 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 and beta power decrease (Logan et al. 2002; Siepmann and Kirch 2002). The vigilance of participants was checked by monitoring EEG parameters such as slowing of the alpha rhythm or appearance of spindles to prevent possible enhancement of the theta power due to drowsiness (Moazami-Goudarzi et al. 2010), and no participants included in the current study showed such drowsiness-related EEG changes.

Source localization analysis

Standardized low-resolution brain electromagnetic tomography (sLORETA), a functional imaging method based on certain electrophysiological and neuroanatomical constraints (Pascual-Marqui 2002), was utilized to estimate the intracerebral sources generating the scalp-recorded electrical activity in each of the following eight frequency bands: delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz), and gamma (30.5–44 Hz) (Song et al. 2013a, b). Because the sLORETA itself corrects for multiple testing (i.e., for the collection of tests performed for all electrodes and/or voxels, and for all time samples and/or discrete frequencies) by conducting random permutations (5,000 permutations in the current study), no further correction is required for multiple comparison (Nichols and Holmes 2002; Pascual-Marqui 2002). In sLORETA, the cortex is modeled as a collection of volume elements (6,239 voxels, size $5 \times 5 \times 5$ mm) and is restricted to cortical gray matter and hippocampi in the digitized Montreal Neurological Institute (MNI) coordinates corrected to the Talairach coordinates, and neuronal activity is computed as current density ($\mu A/mm^2$) without assuming a predefined number of active sources (Fuchs et al. 2002). Scalp electrode coordinates on the MNI brain are derived from the international 5 % system (Jurcak et al. 2007). The sLORETA algorithm solves the inverse problem by assuming related orientations and strengths of neighboring neuronal sources (represented by adjacent voxels).

The sLORETA has proven to be an efficient tool for functional mapping because it is consistent with physiology and capable of correct localization (Pascual-Marqui 2002) and independent validation of the localization properties of sLORETA has been replicated (Wagner et al. 2004; Sekihara et al. 2005). sLORETA has been repeatedly validated by comparing sLORETA with other established localization methods such as positron emission tomography (PET) (Pizzagalli et al. 2004; Zumsteg et al. 2005; Pae et al. 2003), structural magnetic resonance imaging (MRI) (Worrell et al. 2000), and functional MRI (Mulert et al. 2004; Vitacco et al. 2002). 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 subgenual anterior cingulate cortex (sgACC) (Pizzagalli et al. 2004) and the mesial temporal lobe (Zumsteg et al. 2006b) using sLORETA. The version of sLORETA employed here is available at http://www.unizh.ch/keyinst/NewLORETA/LORETA01.htm.

Region of interest analysis

Based on the results of source-localized correlation analysis and group comparison, four region of interests (ROIs) composed of right A1s (BAs 41/42) and A2s (BAs 21/22) separately for the alpha1 and 2 frequency bands were selected and the log-transformed electric current density was averaged across all voxels belonging to these ROIs. In addition, to further better understand the differences between the T+H+ and T+H− groups with regard to these ROIs, 17 individuals who had neither hyperacusis nor tinnitus were collected from a normative database consisting of 235 participants who underwent an EEG analysis. By matching one-by-one to the study participants with regard to age and sex, a normal control group consisting of 15 males and two females with a mean age of 40.2 ± 7.7 years (range 27–53 years) was generated and their mean current densities in the A1/A2 for the alpha1 and two frequency bands were calculated. An analysis of variance (ANOVA) test was performed among the T+H+ group, the T+H− group, and the normal control group, and post hoc independent *t* tests with Bonferroni correction for multiple comparisons were performed to compare the mean current density values separately between the T+H+ and normal control groups, the T+H− and normal control groups, and the T+H+ and T+H− group if the ANOVA test results were significant.

In the same way, to further investigate the differences between the T+H+ and T+H− groups, the mean current densities of the data-driven post hoc ROIs, the bilateral dorsal anterior cingulate cortex (dACC), and the left orbitofrontal cortex (OFC) for the beta band, were calculated and compared among the T+H+/T+H− and normal control groups.

Functional connectivity

The functional organization of the human brain can be described as a network of rich connectivity whereby the neurons (or cortical columns) are seen as nodes within the network and the functional connections between them as edges within this network. One possible method that has been suggested for investigating this large-scale functional connectivity is phase synchronization over multiple frequency bands (Varela et al. 2001; Sauseng and Klimesch 2008). However, methods of phase synchronization measurement are easily contaminated with instantaneous, non-physiological contributions arising from volume conduction and low spatial resolution (Bruder et al. 2012). As a solution for this problem, a refined technique (i.e., Hermitian covariance matrices) that removes this confounding factor considerably has recently been introduced (Pascual-Marqui 2007). This measure of dependence can be applied to any number of brain areas jointly, i.e., distributed cortical networks, whose activity can be estimated with sLORETA. Measures of linear dependence (coherence) between multivariate time series are defined and the measures 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, and they are defined in the above-described eight frequency bands. Based on this principle, lagged connectivity was calculated using the connectivity toolbox in sLORETA. For functional connectivity analysis, a total of 28 ROIs were defined based on previous literature on hyperacusis and tinnitus, and detailed information of these 28 ROIs are described in Table 2. Each ROI consist 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

For all analyses, statistical significance was set at $P < 0.05$. We also report $P < 0.10$ to include trend-level significances. In order to identify neural correlates of hyperacusis under resting state, the log-current density of all 34 participants was correlated with the HQ score using voxel-by-voxel correlation analysis for the eight different frequency bands. Also, to identify potential differences in brain electrical activity between the T+H+ and T+H− groups, voxel-by-voxel analysis using sLORETA was performed for the eight different frequency bands between-condition comparisons of the current density distribution. Non-parametric statistical analyses of sLORETA images (statistical non-parametric mapping; SnPM) were performed for each contrast using sLORETA's built-in voxelwise randomization tests (5,000 permutations) and employing a log-*F*-ratio statistic for independent groups with a threshold of $P < 0.05$, corrected for multiple comparison. A correction for multiple comparisons in SnPM using random permutations (5,000 in the current study) has been proven to give results similar to those obtained from a statistical parametric mapping approach using a general linear model with multiple comparisons corrections derived from random field theory (Holmes et al. 1996; Nichols and Holmes 2002).

For lagged connectivity differences, we compared differences between the T+H+ and T+H− groups for each contrast employing the *t* statistics for independent groups with a threshold $P < 0.05$, also corrected for multiple comparisons by conducting sLORETA-built-in voxelwise randomization tests for all the voxels included in the 28 ROIs for the connectivity analysis (5,000 permutations were performed in the current study).

To further explore the relation between the alpha power in the right A1 and A2 and the beta power in the left OFC

Table 2 Twenty-eight regions of interest and their references

Regions of interest	BA	Centroid voxel[a]			References
		x	*y*	*z*	
Auditory cortex	41L	−46	−29	10	(Jastreboff 1990; Kringelbach 2005; Rolls 2004; Hwang et al. 2009; Levitin et al. 2003)
	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)
	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)
	7R	15	−63	49	

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

[a] Coordinates are described in MNI coordinates

and right dACC, Pearson cross-correlations between the log-transformed electric current densities of the right A1 and A2 and those of the OFC/dACC were calculated and corrected for multiple comparisons separately for the T+H+ and T+H− groups using MATLAB 2010b (The MathWorks, Natick, MA, USA).

Results

Source-localized correlation analysis

sLORETA correlation analysis revealed that the HQ score was positively correlated with the log-transformed current density of the left OFC for the theta frequency band, the right primary/secondary auditory cortices for the alpha1 frequency band, and the dACC for the beta1 frequency band (Fig. 1). No negative correlations between the HQ score and the log-transformed current density were found.

Source-localized group comparison

Compared to the T+H− group, the T+H+ group demonstrated significantly increased activities in the bilateral supplementary motor area (SMA, BA 6) reaching to the bilateral dorsal premotor cortex (dPMC, BA 6) for the beta1 frequency band ($P = 0.03$), the bilateral dACC (BA 24) for beta1/2 ($P = 0.03$ and $P = 0.04$, respectively), and the left OFC (BA 10) for beta3 ($P = 0.03$) (Fig. 2). In addition, the T+H+ group showed increased activity on a trend level in the right A2 (BA 21) for the alpha1 frequency band ($P = 0.09$) and in the right A1 (BA 42) reaching to the right temporo-parietal junction (BA 40) for alpha2 ($P = 0.09$) (Fig. 2, uppermost panels tagged with daggers).

ROI analysis

The sLORETA contrast between T+H+ and T+H− groups yielded relatively increased activity on a trend level

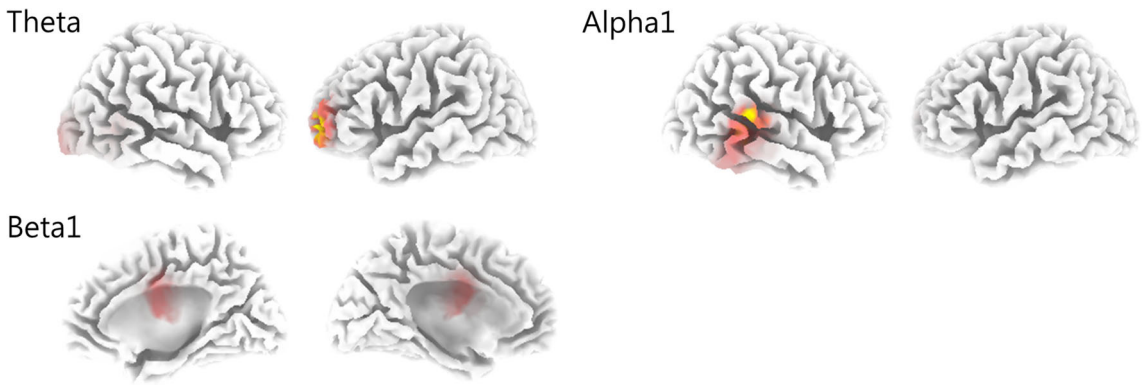

Fig. 1 Standardized low-resolution brain electromagnetic tomography (sLORETA) correlation analysis between the log-transformed current density of all 34 patients and the hyperacusis questionnaire (HQ) score. The left orbitofrontal cortex for the theta frequency band, the right primary/secondary auditory cortices for the *alpha1* frequency band, and the dorsal anterior cingulate cortex for the *beta1* frequency band showed positive correlations with the HQ score

in the right secondary auditory cortex (A2) for the alpha1 and in an area of the right primary auditory cortex (A1) reaching to the temporo-parietal junction for the alpha2 frequency band in the T+H+ group as compared to T+H− group. These results were in contrast to previous studies indicating that tinnitus is characterized by a reduction in alpha power as compared to normal controls (Raz and Rodrigue 2006; Weisz et al. 2005, 2007). The ROI analysis using log-transformed mean current density for the alpha1 frequency band at BA 41, 42, 21, and 22 in the T+H+ group showed a higher tendency than that of the T+H− group, but without statistical significance on ANOVA (Fig. 3). However, the log-transformed mean current densities for the alpha2 frequency band showed significance on ANOVA for all A1 and A2 except for BA 21 ($P = 0.03$, $F = 3.89$ for BA 41, $P = 0.02$, $F = 4.11$ for BA 42, $P = 0.03$, $F = 3.89$ for BA 41, and $P = 0.03$, $F = 3.94$ for BA 22). The post hoc *t* tests (with Bonferroni correction for multiple comparisons) revealed that the log-transformed mean current densities for the alpha2 frequency band in the T+H+ group were significantly higher than those in the T+H− at BA 41 (2.69 ± 1.07 vs. 1.86 ± 0.81, $t = 2.55$, $P = 0.02$, $df = 29.75$), BA 42 (2.65 ± 1.08 vs. 1.76 ± 0.81, $t = 2.72$, $P = 0.01$, $df = 29.62$), and BA 22 (2.53 ± 1.06 vs. 1.69 ± 0.78, $t = 2.64$, $P = 0.01$, $df = 29.44$) (Fig. 3). While the comparison of the current density at these four ROIs between the T+H+ group and the normal control group yielded no significant differences for the alpha1 and two frequency bands, the T+H− group revealed significantly decreased current density as compared to the normal control group at BAs 41 and 22 for the alpha2 frequency band (Fig. 3). In brief, we found significantly higher activation of the right A1 and A2 in the T+H+ group relative to the T+H− group for the alpha2 frequency band by the ROI analysis including the normal control group, although the difference did not reach statistical significance using the sLORETA whole brain analysis.

Meanwhile, another ROI analysis using the log-transformed mean current density for the beta1/2 frequency bands at bilateral BA 24 and beta3 frequency band at left BA 10 showed no statistically significant differences among the three groups on ANOVA (Fig. 4).

Functional connectivity

The functional connectivity analysis yielded significant differences between the T+H+ and T+H− groups for the beta3 frequency band ($P < 0.05$). The T+H+ group revealed increased functional connectivity as compared to the T+H− group from the right A2 to the right A1, right OFC and to the left sgACC. Increased connectivity of the T+H+ group for the beta3 frequency band was also found between the left A1 and the left posterior cingulate cortex (Fig. 5).

For the other seven frequency bands, no significant differences could be obtained between the two control groups by the contrast "the T+H+ group—the T+H− group".

Cross-correlation analysis

Pearson cross-correlation analyses demonstrated higher correlation between the alpha2 power of the right A1 and the beta3 power of the left OFC in the T+H+ group (Fig. 6, upper left panel) as compared to the T+H− group (Fig. 6, upper middle panel). Meanwhile, the correlation between the alpha2 power in the right A1 and the beta1 and two powers in the right dACC showed no significant differences between the two groups (Fig. 6, lower left and middle panels).

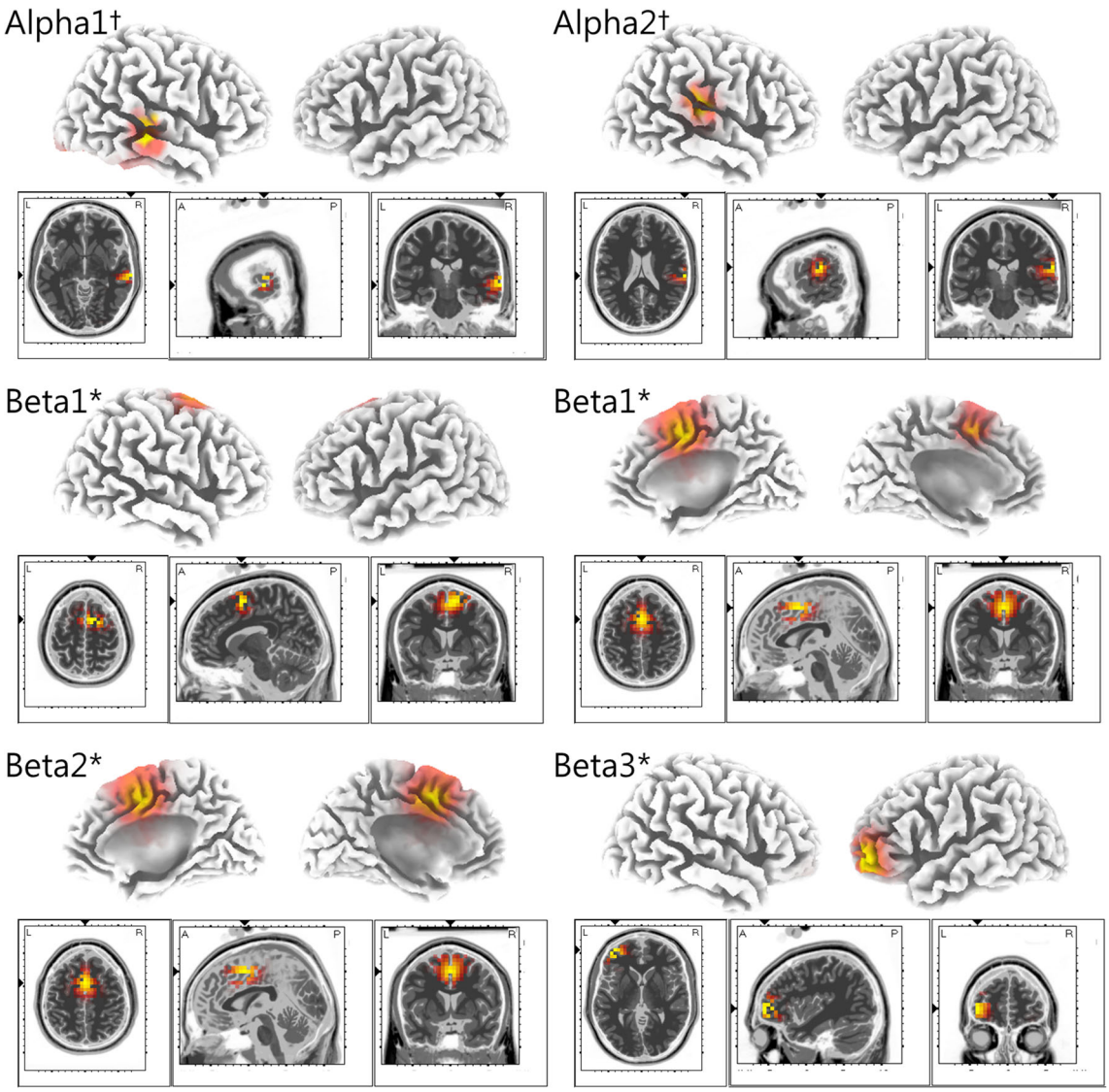

Fig. 2 Standardized low-resolution brain electromagnetic tomography (sLORETA) contrast analysis between the tinnitus with hyperacusis (T+H+) and tinnitus without hyperacusis (T+H−) groups. Compared to the T+H− group, the T+H+ group demonstrated significantly increased activities (*asterisks*) in the bilateral supplementary motor area, bilateral dorsal anterior cingulate cortex, and left orbitofrontal cortex for the beta frequency bands. In addition, the T+H+ group showed increased activities on a trend level (*daggers*) in the right auditory cortices for the alpha bands

Discussion

Hyperacusis was originally regarded as a compensatory mechanism for acquired hearing loss. Animal experiments supported this theory, showing transient enhancement on the evoked AC response induced by noise over-exposure (Sun et al. 2008) and increased central neural gain by systemic injection of salicylate (Sun et al. 2009). In humans, transient hyperacusis could be induced in participants with normal hearing threshold by wearing earplugs for 2 weeks (Formby et al. 2003) and in hyperacusic participants with normal hearing the amount of activation produced by auditory stimuli was better correlated with the perceived loudness of the sound stimuli than to their actual level (Hall et al. 2001). In this regard, an active loudness model has been suggested in which hyperacusis is explained as increased nonlinear gain (Zeng 2013). In short, however, most of the explanations are speculative and the exact mechanism of hyperacusis is still missing (Eggermont 2013).

In the current study, we attempted to find clues for the neural correlates of hyperacusis by qEEG-derived cortical activity in the resting state. In brief, HQ was positively correlated with the activity in the left OFC for the theta band, in the right A1/A2 for the alpha1, and in the dACC for the beta1. We also found increased activity in the dACC for

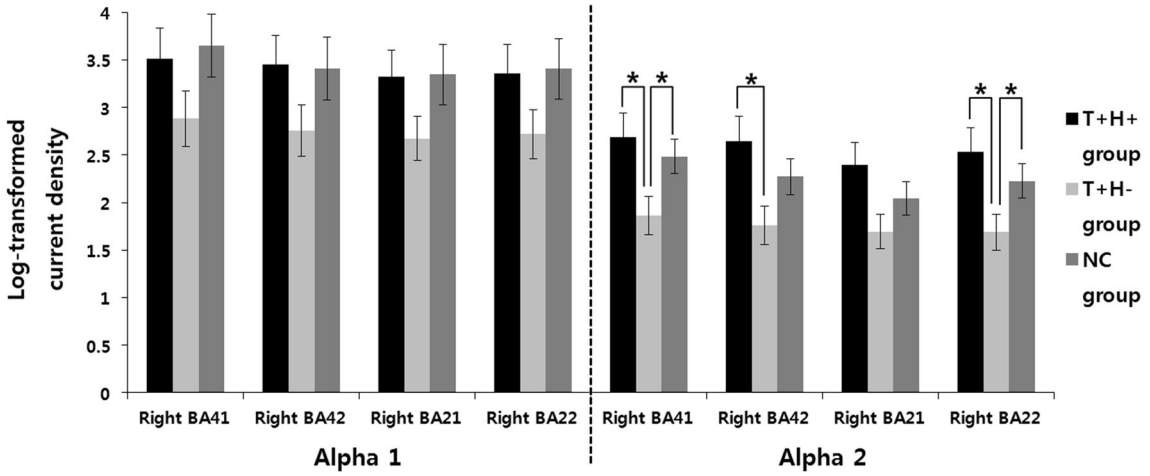

Fig. 3 Region of interest (ROI) analysis for the right primary/secondary auditory cortices (A1/A2) for the alpha frequency bands. Log-transformed mean current densities of the T+H+ group were significantly higher as compared to the T+H− group in the right A1 and A2 for the alpha2 band. There were no significant differences between the T+H+ group and the normal controls. *Error bars* designate standard errors

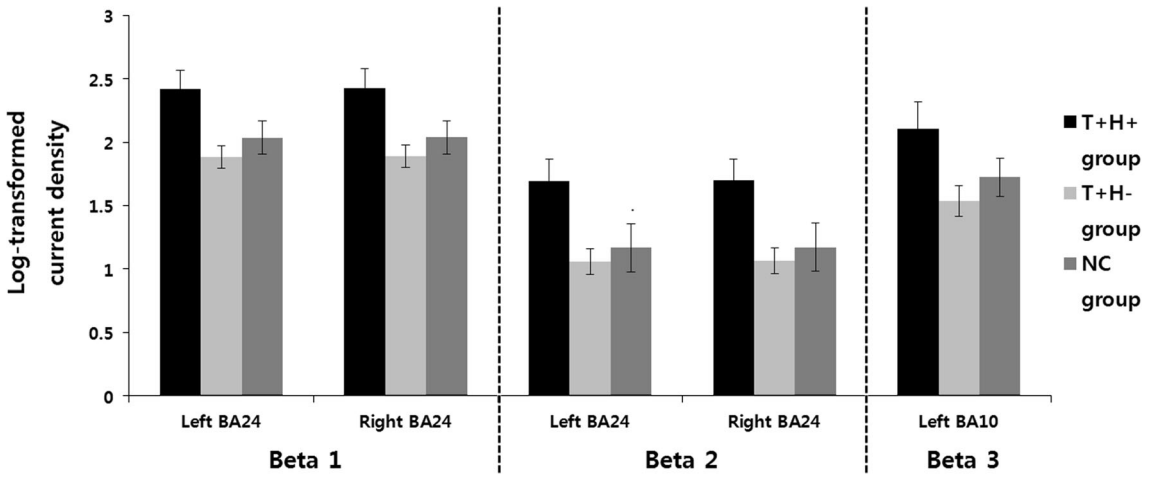

Fig. 4 Region of interest (ROI) analysis for the bilateral dorsal anterior cingulate cortices (dACCs) for the beta1 and 2 bands and for the left orbitofrontal cortex (OFC) for the beta3 band. Log-transformed mean current densities showed no significant differences among the three groups on ANOVA

the beta1 and two frequency bands, in the bilateral SMA and dPMC for beta1, and in the left OFC for beta3 in the T+H+ group as compared to the T+H− group. In addition, relatively increased activity as compared to the tinnitus group without hyperacusis was also found in right A1 and A2 for the alpha2 band by the ROI analysis. Functional connectivity analysis further revealed increased connectivity from A2 to A1, the sgACC, and the OFC for the beta3 frequency band (for summary, see Fig. 7).

Resting-state hyperactivity of the hyperacusis brain

Literally, the term "hyperacusis" designates hyperresponsiveness to sound stimuli. Previous functional neuroimaging studies thus utilized sound stimuli such as music, pure tone, or white noise to explore neural correlates of hyperacusis in human participants (Hwang et al. 2009; Gu et al. 2010; Levitin et al. 2003). However, to the best of our knowledge, no study has been conducted to investigate ongoing cortical activity differences in the hyperacusis brain. The current study, revealing remarkable differences between the T+H+ group and the T+H− group, may indicate hyperacusis-related unique cortical activities even in the resting state without any sound stimulation. In the following sections, we address possible functions of the regions indicating relative activation and increased connectivity in the T+H+ group.

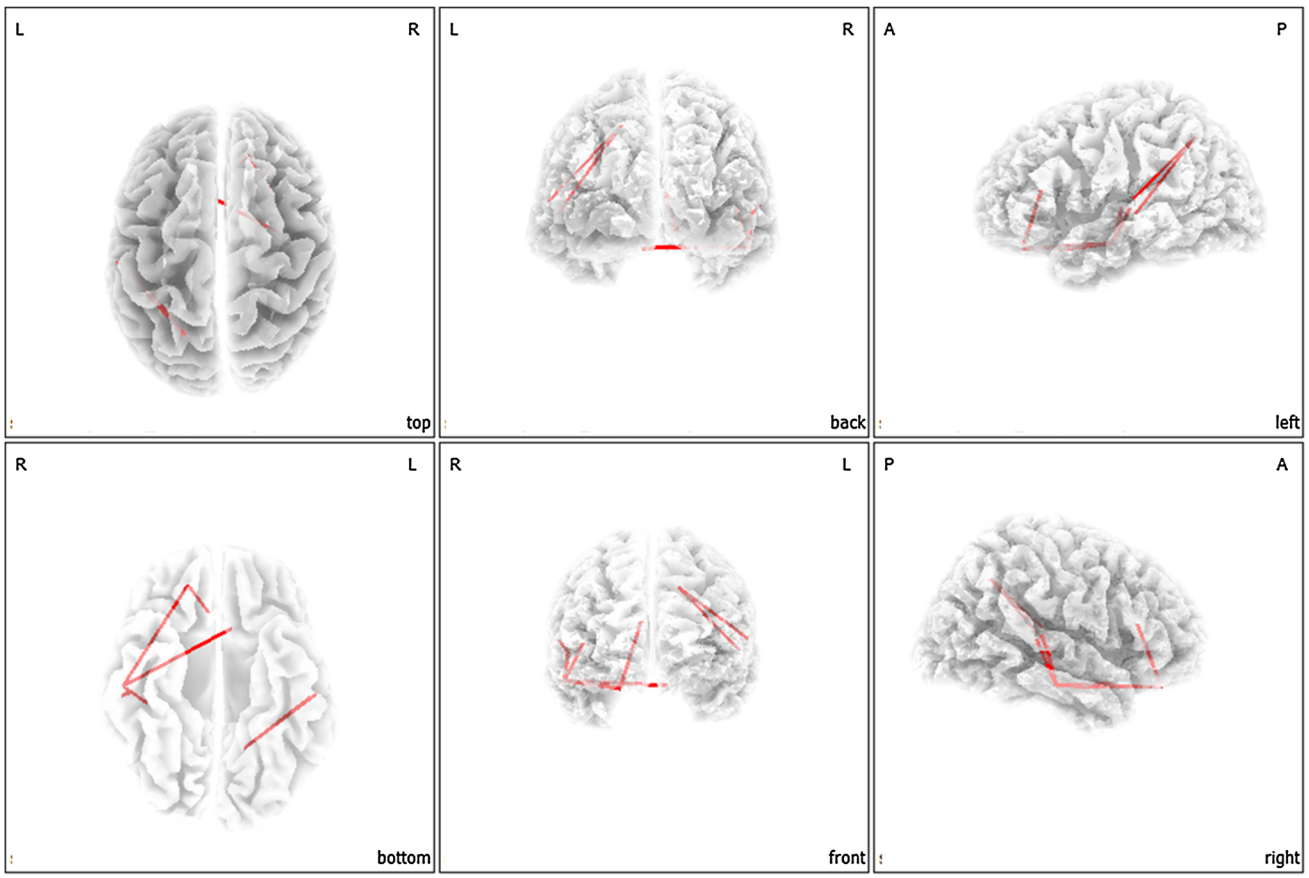

Fig. 5 Connectivity contrast analysis between the T+H+ and T+H− groups. The T+H+ group demonstrated increased functional connectivity as compared to the T+H− group from the right A2 to the right A1, right OFC, and to the left subgenual anterior cingulate cortex (sgACC). Increased connectivity of the T+H+ group for the beta3 frequency band was also found between the left A1 and the left posterior cingulate cortex

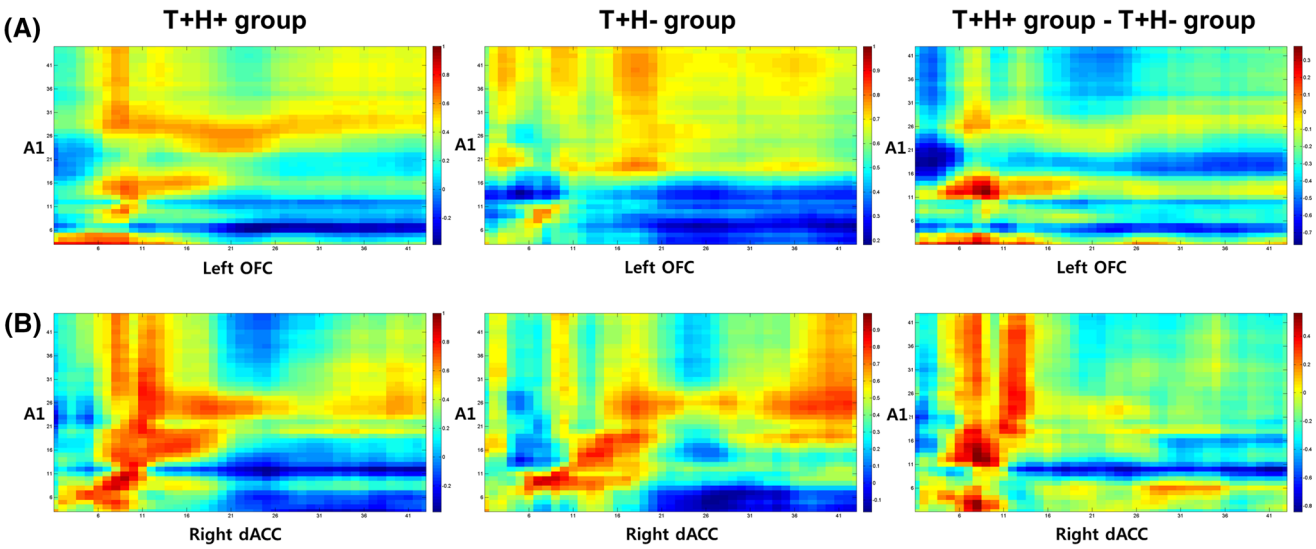

Fig. 6 Cross correlation analyses of the log-transformed mean current densities between the right primary auditory cortex (*A1*) and the left orbitofrontal cortex (*OFC*) (*upper panels*) as well as between the right A1 and the right dorsal anterior cingulate cortex (*dACC*) (*lower panels*). Note that the alpha2 power in the right A1 and the beta power in the left OFC reveal higher correlation in the T+H+ group as compared to the T+H− group

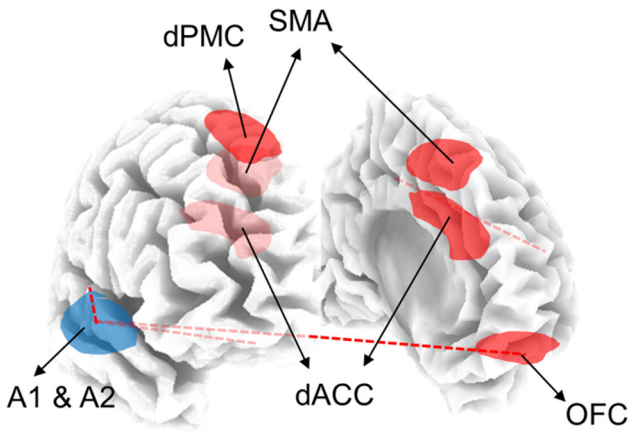

Fig. 7 Schematic summary of the areas with increased and decreased activities in the T+H+ group as compared to the T+H− group. *SMA* supplementary motor area, *dPMC* dorsal premotor cortex, *A1/2* primary/secondary auditory cortices, *dACC* dorsal anterior cingulate cortex, *OFC* orbitofrontal cortex

Constantly enhanced vigilance to auditory stimuli due to the increased activity in the dACC and OFC

Cued prediction of the occurrence of a nociceptive event reliably elicits a potentiation of a fear response characterized by increased autonomic arousal and defensive response mobilization (Hamm and Weike 2005; Hamm and Vaitl 1996). Together with frequently suggested components of this neural network such as the amygdala and the insula, two notable brain regions, the dACC and the OFC, are constantly indicated as the key areas of activation when anticipating an interoceptive threat. The dACC and the OFC have been found to be activated during anticipation of noxious stimuli in several studies (Kalisch et al. 2006; Kalisch et al. 2005; Holtz et al. 2012; Nitschke et al. 2006; Atlas et al. 2010), and the activation of these two regions was more sustained in high fear compared to low fear persons (Holtz et al. 2012). In a recent meta-analysis of fear studies, consistently significant activation in response to the warning cue was found in a large cluster including the dACC and this cluster was interpreted as an index of increased appraisal of the warning cues (Mechias et al. 2010). Another recent study in primates demonstrated suppression of the spontaneous recovery of aversive memories by depressing the dACC activity with low frequency stimulation (Klavir et al. 2012).

In this regard, the results of the current study showing relatively increased activity in the dACC/OFC may connote constantly increased vigilance for sound stimuli leading to increased reflex to sound stimuli only in the T+H+ group. This is in line with earlier work showing that prestimulus activation of the dACC, a component of the intrinsic alertness network (Dosenbach et al. 2007; Boly et al. 2007), is associated with increased sensitivity to external auditory stimuli (Sadaghiani et al. 2009). In this sense, increased resting dACC activity may also render a subject hyperacusic by increasing sensitivity to forthcoming sound stimuli.

The relatively increased activity in the SMA/dPMC for the beta1 frequency band may be interpreted as the priming of flight behavior. The link between the sensorimotor system and affective/cognitive function has been explained by the embodied cognition theory (Garbarini and Adenzato 2004). In the context of the embodied cognition theory, the constant anticipation of environmental sound stimuli may evoke simulated motor action to avoid nociception. The SMA plays a role in preparing voluntary movement (Cunnington et al. 2005), and an increased activation in this area during the confrontation with the feared object may reflect participants' urge to avoid the anticipated stimuli (Scharmuller et al. 2011). From this viewpoint, the activation of the SMA/dPMC may reflect prepared avoidance of sound stimuli in participants with hyperacusis.

Top-down inhibition of the resting-state auditory cortical activity

The processing of auditory stimuli involves a reduction of auditory alpha power (Lehtela et al. 1997), and especially this auditory alpha reduction is marked in tinnitus subjects (Weisz et al. 2005, 2011). The current study revealing decreased alpha2 activity in the T+H− group as compared to the normal control group by the ROI analysis thus replicates previous literature. By contrast, the HQ was positively correlated with the activity in the A1/A2 for the alpha1 frequency band. Since growing evidence from EEG (Alper et al. 2006; Klimesch 1999) and magnetoencephalography (Weisz et al. 2007) studies suggests that alpha rhythms reflect the excitatory–inhibitory balance within sensory/motor regions with strong alpha power, indicating an inhibitory state, we may regard the positive correlation and the increased alpha power in the T+H+ group as a relative inhibition of the AC in more hyperacusic patients. As the mean current density of the ROIs was not significantly different between the T+H+ group and the normal control group, we surmise that presumed alpha power reduction by tinnitus may have been counterbalanced by hyperacusis in the T+H+ group.

Previous human studies on hyperacusis have yielded inconsistent results. A functional magnetic resonance imaging (fMRI) study revealed relatively decreased AC activity by sound stimuli in hyperacusic Williams syndrome patients as compared to normal controls (Levitin et al. 2003), while another voxel-based morphometry study revealed relatively preserved grey matter volume in sematic dementia patients with tinnitus or hyperacusis as compared to semantic dementia patients with no history of

hyperacusis (Mahoney et al. 2011). Meanwhile, as aforementioned, previous animal research using hyperacusic animal models demonstrated enhanced responsiveness of the AC by showing increased sound-evoked potentials in the AC and increased spike firing rates of AC neurons (Norena et al. 2010; Sun et al. 2012). In sharp contrast to these results from animal studies, the current study showed increased alpha in the AC in the resting state. In short, the AC of the hyperacusis brain may be hypoactive in the resting state without any sound stimuli while hyperactive when stimulated by sound.

One possible explanation for the relatively increased alpha power in the right AC may be a top-down suppression of the low-level sensory cortex, that is, constant anticipation of aversive sound stimuli may have resulted in top-down deactivation of the AC in the resting state. In a study utilizing cues either "to-remember" or "not-to-remember" visual stimuli that could later be asked to be retrieved, non-remember cues elicited pronounced top-down alpha increase as opposed to remember cues (Freunberger et al. 2009). Considering that forthcoming sound stimuli are "not-to-hear" aversive auditory stimuli to the T+H+ participants, they may have modulated auditory alpha power by a top-down alpha increase in the silent environment to cope with sound-evoked distress.

Pearson cross-correlation demonstrated higher correlation between the alpha2 power in the right A1 and the beta3 power in the left OFC in the T+H+ group as compared to the T+H− group. In addition, the left OFC revealed increased connectivity to the right A2 for the beta3 band. In this regard, the left OFC may be the center of the top-down modulation of the auditory alpha power in hyperacusis. The OFC, the highest order associative cortical region of the brain, is frequently implicated in top-down processing of emotion (Wright et al. 2008; O'Doherty 2004) and the reward or affective value of the earliest cortical areas for taste, touch, texture, and face expression (Grabenhorst et al. 2008; Rolls and Grabenhorst 2008). Also, the OFC is suggested to be a key pain-processing region reflecting a combination of nociceptive input and top-down information related to expectations and anticipatory processes (Atlas et al. 2010). Notably, the OFC was suggested to exert top-down encoding of auditory information (Frey et al. 2004). From this viewpoint, the OFC may be activated by anticipation of aversive sound stimuli as aforementioned, and at the same time it may function as a top-down suppressor of the AC as a coping mechanism against hyperacusis.

Hyperacusis and allodynia/hyperalgesia

As mentioned above, allodynia and hyperalgesia have been frequently compared to hyperacusis based on the analogy of exaggerated response to innocuous or minimally aversive somatic stimuli. Many studies have focused on defining the cortical network involved in allodynia/hyperalgesia, but the results obtained have been very variable, reflecting etiological heterogeneity, lesion topography, symptoms, and stimulation paradigms (Moisset and Bouhassira 2007).

However, intriguing similarities between the current study and previous research on allodynia/hyperalgesia can be found. For instance, the OFC has been frequently found to be activated by allodynia-evoking stimulation (Witting et al. 2001; Kramer et al. 2008). The dACC activity change has also been found in most of the imaging studies on allodynia/hyperalgesia, but some studies revealed increased dACC activity (Lanz et al. 2011; Witting et al. 2006) while other studies showed a 'paradoxical' decrease in dACC activity (Jones and Derbyshire 1997; Rosen et al. 1994; Peyron et al. 2000). In contrast to these discrepant results, a recent meta-analysis of 21 studies on allodynia/hyperalgesia demonstrated increased activity in the ACC and prefrontal cortex, and hypothesized an increased baseline activity during the presence of central sensitization (Lanz et al. 2011). Although none of the included studies in this meta-analysis evaluated resting-state cortical activity, the cortical areas found and the deductive hypothesis of baseline hyperactivity are in accordance with the results of the current study. Another study suggested the upregulation of activity in the OFC as the stronger emotional load of neuropathic pain and higher computational demands of sensory processing (Witting et al. 2006). In addition, participants who were familiar with allodynia activated the ACC and prefrontal cortex as well as the secondary sensory somatosensory cortex only by imagining allodynia during tactile stimulation (Kramer et al. 2008). In this regard, hyperacusis and allodynia/hyperalgesia may share a common network for hyperresponsive behavior. As seen in the current study, a "hyperresponsiveness network" comprising resting-state hyperactivity of the OFC and dACC may be responsible for hyperacusis, and also for allodynia/hyperalgesia. By exploring resting-state cortical activity in participants with allodynia/hyperalgesia, this perspective may be validated.

Limitation of the study has to be mentioned. First, even though tinnitus-related characteristics were near-totally matched, still the results may have been affected by tinnitus-related cortical activity changes. Future studies utilizing purely hyperacusic patients should be performed to confirm our findings. Second, the current study was conducted retrospectively utilizing our resting-state EEG database, we could only reveal ongoing resting-state cortical activities related to hyperacusis. Because hyperacusis itself is a sound-driven phenomenon and we have found intriguing features under resting-state in participants with hyperacusis, future prospective studies utilizing sound

stimuli-evoked cortical responses as well as resting-state ongoing cortical activities should be performed to reveal changes in the cortical oscillation pattern. Third, we found lateralized effects (increased left OFC activity and increased right A1/A2 activity). As the HQ adopted in the current study does not evaluate the left and right ear separately, these effects might have been originated from lateralized hyperacusis of the enrolled participants. Future studies addressing possible lateralized hyperacusis should be performed to clearly address this issue. Fourth, significant effects in the OFC for the beta band may have been partially influenced by electromyogram (EMG) contamination (Fu et al. 2006; Goncharova et al. 2003). Although we have cleaned out all episodic artifacts from the EEG stream by visual inspection and the application of ICA, and the removal of muscle artifact in scalp-based recordings has been validated (McMenamin et al. 2010; Keren et al. 2010), EMG contamination should be further checked by performing future studies to replicate the current findings.

In conclusion, the characteristics of the participants with hyperacusis could be described as resting-state increased beta activity in the OFC/dACC as well as increased alpha power in the right AC. The increased OFC/dACC activity may be ascribed to constantly enhanced resting-state vigilance and top-down inhibition of the resting-state AC in tinnitus patients with hyperacusis. These findings as well as previous literature on allodynia/hyperalgesia may suggest a possible default hyperresponsive network, which may be used for developing a neuromodulation treatment strategy for these disease entities.

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