Hearing Research 411 (2021) 108356

Contents lists available at ScienceDirect

Hearing Research

journal homepage: www.elsevier.com/locate/heares

Is the posterior cingulate cortex an on-off switch for tinnitus?: A comparison between hearing loss subjects with and without tinnitus

Sang-Yeon Lee[a,1], Munyoung Chang[b,1], Byungjoon Kwon[c], Byung Yoon Choi[a], Ja-Won Koo[a], Taesup Moon[d], Dirk De Ridder[e], Sven Vanneste[f], Jae-Jin Song[a,*]

[a] Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University Bundang Hospital, Seongnam, Gyeonggi-do, 13620, Korea.
[b] Department of Otorhinolaryngology-Head and Neck Surgery, College of Medicine, Chung-Ang University, Seoul, Korea
[c] NCSoft Game AI Lab, Seongnam, 13494, South Korea
[d] Department of Electrical and Computer Engineering, Seoul National University, Seoul, Korea
[e] Unit of Neurosurgery, Department of Surgical Sciences, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand
[f] Lab for Clinical & Integrative Neuroscience, Trinity College of Neuroscience, Trinity College Dublin, Ireland

ARTICLE INFO

Article history:
Received 30 October 2020
Revised 14 August 2021
Accepted 20 September 2021
Available online 24 September 2021

Keywords:
Bayesian
Circuit breaker
Default mode network
Hearing loss
Tinnitus

ABSTRACT

As the human brain works in a Bayesian manner to minimize uncertainty toward external stimuli, the deafferented brain may generate tinnitus in an attempt to fill in missing auditory information, e.g. due to hearing loss. However, not everybody with hearing loss develops tinnitus. Understanding the differences between people with hearing loss who develop tinnitus versus those who do not offers a unique opportunity to unravel critical brain areas involved in the generation of a phantom sound. In this study, we compared resting-state quantitative electroencephalography between hearing loss patients with (HL-T) and without tinnitus (HL-NT) to identify cortical oscillatory signatures that may reveal prerequisites for the selective development of tinnitus in subjects with hearing loss. We enrolled 65 subjects with HL-NT and 65 subjects with HL-T whose tinnitus handicap inventory scores were <16 (grade 1) to minimize the bias induced by distress-induced cortical activity changes. Subjects in the HL-T and HL-NT groups were matched in terms of the bilateral hearing threshold (0.25–8 kHz) using nearest neighbor method. Compared to the HL-NT group, the HL-T group showed significantly higher activity in the right parahippocampus for the beta 1 frequency band, in the left inferior parietal lobule (IPL) for the beta 2 frequency band, and in the right IPL for the beta 3- and gamma frequency bands. Functional connectivity analyses revealed that the HL-T group had significantly higher connectivity than the HL-NT group between both parahippocampal gyri and the right IPL for the delta frequency band, and between the left posterior cingulate cortex (PCC) and right IPL for the beta 2 frequency band. These results suggest that tinnitus may be perceived only if auditory memory stored in the parahippocampus is actively linked to the IPL-based "circuit breaker" system and the circuit breaker signal is connected to the PCC-based default mode network (DMN). Thus, when the circuit breaker system regards tinnitus secondary to peripheral deafferentation as a salient event and then the DMN regards tinnitus as a norm, subjects with hearing loss may consciously perceive tinnitus. The results of this study further refine the recently proposed Bayesian model and decipher the neurobiological mechanism of the selective development of tinnitus in subjects with hearing loss.

1. Introduction

Tinnitus is a conscious auditory perception in the absence of an external stimulus; it is considered a phantom auditory perception due to the lack of a corresponding physical sound source (Lee et al., 2020a; Vanneste et al., 2018a). The prevalence of chronic tinnitus is approximately 15% worldwide (Pinto et al., 2014). In most cases, tinnitus is accompanied by some degree of hearing loss (HL) (De Ridder et al., 2014c; Rauschecker et al., 2010; Schecklmann et al., 2012; Song et al., 2017).

Because tinnitus pitch and the frequency of maximum HL are closely correlated (Norena et al., 2002; Schecklmann et al., 2012), tinnitus generation may be closely linked to preceding peripheral HL. Previous studies have shown that peripheral auditory deafferentation increases spontaneous neuronal firing in the central auditory system and induces cortical maladaptive plastic changes in

* Corresponding author.
E-mail addresses: jjsong96@snubh.org, jjsong96@gmail.com (J.-J. Song).
[1] These two authors contributed equally to this work.

https://doi.org/10.1016/j.heares.2021.108356
0378-5955/

auditory and non-auditory regions (Rauschecker et al., 2010). Conversely, enriched acoustic stimulation and dynamic peripheral reafferentation by cochlear implantation in subjects with profound HL abates tinnitus (De Ridder et al., 2014c; Song et al., 2017). These findings suggest that peripheral HL may act as a prerequisite to the generation of tinnitus.

In a previous study, a congenital unilateral deaf animal model has revealed that a tonotopic map leading to a corresponding auditory memory is essential for generating tinnitus (Eggermont et al., 2016). As the human brain works in a Bayesian manner to minimize uncertainty for external stimuli based on memory, a brain with peripheral auditory deafferentation may attempt to fill in the missing auditory information by generating tinnitus (De Ridder et al., 2014b; Lee et al., 2017). A subsequent theoretical multiphase compensation model also suggested that tinnitus is likely the result of maladaptive cortical plasticity, depending on the amount of HL (Vanneste et al., 2016). This model indicated that in subjects with moderate to severe HL, tinnitus is associated with a parahippocampal mechanism because uncertainty cannot be overcome by neural plasticity or tonotopic reorganization within the auditory cortex (De Ridder et al., 2014a; Vanneste et al., 2016).

However, not all people with HL do develop tinnitus, so there must be another factor that switches tinnitus on in people with HL. Previously, it was observed that subjects with HL and tinnitus exhibited different psychoacoustic features in terms of frequency selectivity and compression compared to those without tinnitus (Tan et al., 2013), indicating that different cortical mechanisms may be responsible for the perception of auditory phantoms among those with HL, depending on the presence or absence of tinnitus, although differences in frequency selectivity and compression could arise in the auditory periphery. A resting-state functional magnetic resonance imaging study reported significantly higher functional connectivity between limbic regions and the auditory and dorsal attention networks in subjects with HL and tinnitus, compared to those without tinnitus (Schmidt et al., 2013a). However, these findings should be interpreted carefully because pathognomonic oscillatory activity differences have never been investigated in HL subjects with and without tinnitus, where the hearing thresholds are matched between groups. In addition, the findings of previous studies that investigated the linkage between HL and tinnitus may have been affected by cortical activity changes induced by tinnitus-related distress.

In the present study, we compared resting-state quantitative electroencephalography (rs-qEEG) data between subjects with HL with (HL-T) and without tinnitus (HL-NT) to identify cortical oscillatory signatures that may be prerequisites for tinnitus perception in subjects with HL. An important innovation of this study is that we matched both groups in terms of hearing thresholds across all frequencies using a more principled quantitative metric, as opposed to the manual matching heuristics that had been conducted in most of the previous work. Namely, we used the root-mean-squared-error (RMSE) for computing distances between the subjects with HL-T and HL-NT, and the subjects in the HL-T group were sorted by computing the average RMSE with all subjects in the HL-NT group to find the nearest neighbors.. Individuals in the HL-T group were included only if their tinnitus handicap inventory (THI) scores were <16 (Grade 1), indicating that they were minimally affected by distress-induced cortical activity changes. Using whole-brain source localization analyses complemented by functional connectivity analyses, we explored the mechanism of selective tinnitus development in subjects with HL. Our a priori hypothesis was that, as compared to the HL-NT group, the HL-T group would show increased source-localized activity or functional connectivity in areas such as the parahippocampus, based on previous reports of ours (Vanneste et al., 2016; Vanneste et al., 2019).

2. Materials and Methods

2.1. Participants

We retrospectively reviewed the records of subjects with HL who had visited the outpatient clinic at Seoul National University Bundang Hospital (SNUBH) between July 2018 and December 2019. Only subjects whose audiograms met the criteria of having a mean hearing threshold (average of the pure tone audiometry [PTA] thresholds at 500, 1,000, 2,000, and 4,000 Hz) $>$ 40 dB HL as well as high-frequency specific HL (hearing threshold $>$ 40 dB HL at 4 and/or 8 kHz) were included. Among these, HL subjects without tinnitus (the HL-NT group) were initially selected. Subjects with otologic disorders such as otosclerosis or Meniere's disease, psychiatric or neurological disorders, chronic headache, current psychotropic/central nervous system-active medications, history of drug/alcohol abuse, and/or history of head injury (with loss of consciousness) or seizures were excluded from the study. Ultimately, a total of 65 HL-NT subjects were enrolled (**Fig. 1**).

Additionally, 65 subjects with HL and subjective tinnitus (the HL-T group; (no pulsatile, typewriter, or other types of tinnitus subjects were included) with a THI score $\leq$ 16 (Grade 1) to be minimally affected by distress-induced cortical activity changes (Chen et al., 2017; Golm et al., 2013; Milner et al., 2020; Vanneste et al., 2010). For an ideal comparison between the HL-T and HL-NT groups, HL-T subjects with "absolutely no distress" could have been desirable, but this is not feasible in our clinical setting and thus we have recruited "Grade 1" subjects with minimal distress. Also, subjects in the HL-T group were included from the SNUBH database (1,007 rs-qEEG-available subjects) by matching bilateral hearing thresholds (from 0.25 kHz to 8 kHz) to those of the HL-NT group using a more principled quantitative metric, as opposed to the manual matching heuristics that had been conducted in most of the previous work. Namely, we used the root-mean-squared-error (RMSE) for computing distances between the subjects with HL-T and HL-NT, and the subjects in the HL-T group were sorted by computing the average RMSE with all subjects in the HL-NT group to find the nearest neighbors. More specifically, for each Grade 1 HL-T subject in the SNUBH database, we calculated the distance of hearing threshold scores (across 7 frequency bands for each ear) to the scores of all 65 subjects in the HL-NT group. Then, we selected the 65 subjects with the lowest distances (nearest neighbor method). Furthermore, the same exclusion criteria as in the HL-NT group were applied to the HL-T group (**Fig. 1**). Both the HL-T and HL-NT groups showed normal distribution with regard to the THI scores. The protocols of this study were approved by the SNUBH Institutional Review Board (IRB-B-2006-621-105). This study was conducted in accordance with the Declaration of Helsinki.

2.2. Audiological and psychoacoustic evaluation

The hearing thresholds for seven different octave frequencies (0.25, 0.5, 1, 2, 3, 4, and 8 kHz) were evaluated using pure-tone audiometry in a soundproof booth (Lee et al., 2020d). The mean hearing threshold was calculated using the average of the hearing thresholds at 0.5, 1, 2, and 4 kHz (Huh et al., 2020). At each subject's initial visit, we obtained a structured history of their tinnitus characteristics including presence, laterality, and psychoacoustic nature (pure-tone or narrow-band noise).

2.3. EEG recording

To identify the neural substrates associated with tinnitus in subjects with HL, we performed data acquisition and pre-processing procedures as previously reported (Han et al.,

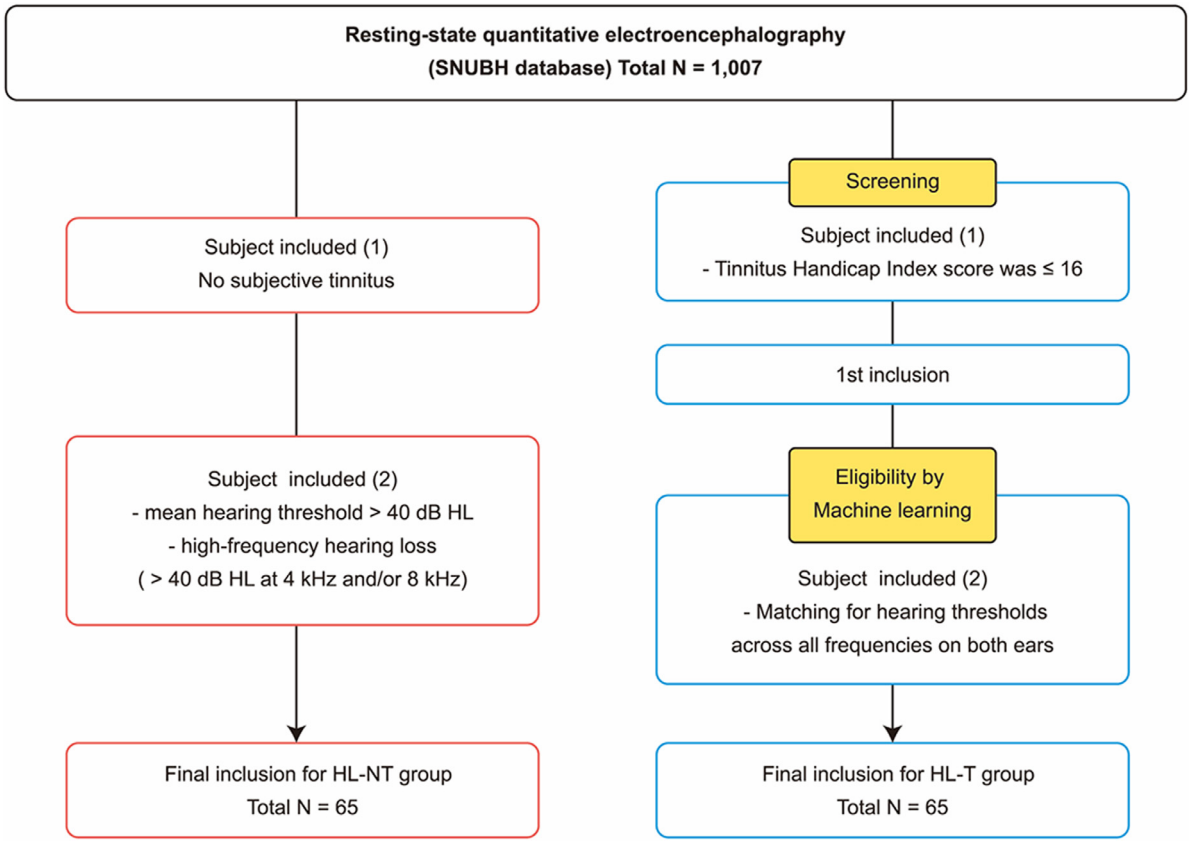

Figure 1. Flow diagram of the inclusion and exclusion criteria for hearing loss with tinnitus (HL-T) group and matched hearing loss without tinnitus (HL-NT) group from a large-scale resting-state quantitative electroencephalography (EEG) database.

2018; Han et al., 2020a; Lee et al., 2019; Song et al., 2017; Vanneste et al., 2018a). Before measurement, the participants were asked not to drink alcohol for 24 h before EEG recording and to avoid caffeinated beverages on the day of recording to prevent alcohol-induced changes in the EEG signal (Korucuoglu et al., 2016) or caffeine-induced reductions in alpha and beta power (Siepmann et al., 2002). The EEGs were recorded with the patient seated upright with eyes closed for 5 min as in recent literature (Lan et al., 2020; Souza et al., 2020; Zhang et al., 2020a; Zhang et al., 2020b) using a tin-electrode cap (ElectroCap, Eaton, OH, USA) and a Mitsar amplifier (EEG-201; Mitsar, St. Petersburg, Russia) in a fully lit room shielded against sound and stray electric fields. More specifically, the EEGs were recorded while the subject seated alone in the soundproof booth used as for regular audiometry that was also shielded against stray electrical fields. Neither a running computer equipment nor other persons were present in the booth during testing. Also, all the power lines were also completely filtered. The EEG data were obtained using WinEEG software ver. 2.84.44 (Mitsar; http://www.mitsar-medical.com). The impedances of all electrodes were maintained at <5 kΩ. Data were obtained at a sampling rate of 1024 Hz and then filtered using a high-pass filter with a cutoff of 0.15 Hz and a low-pass filter with a cutoff of 200 Hz. After initial data acquisition, the raw data were resampled at 128 Hz and then band-pass filtered using a fast Fourier transformation filter with a Hanning window of 2–44 Hz. The data were imported into the Eureka! software (Sherlin et al., 2005) and all episodic artifacts such as eye movement, blinking, teeth clenching, or body movement were evaluated manually and removed from the EEG stream. We eliminated additional artifacts via independent component analyses using the ICoN software (http://sites.google.com/site/marcocongedo/software/nica) (Koprivova et al., 2011; White et al., 2012) to perform blind source separation (BSS) methods that are ideally suited for minimizing the effects of volume conduction in noninvasive EEG recordings, allowing more accurate localization of deep brain processes. Because the vigilance level of the subject can affect data interpretation, we meticulously monitored abnormal EEG patterns. This monitoring process included slowing of the alpha rhythm or the emergence of sleep spindles. No participants exhibited any abnormal EEG patterns during measurement.

2.4. Source localization analyses

We used standardized low-resolution brain electromagnetic tomography (sLORETA; http://www.uzh.ch/keyinst/NewLORETA/Software/Software.htm) to estimate the intracerebral sources that generated scalp-recorded electrical activity. The sLORETA software includes a toolbox for the functional localization of standardized current densities based on electrophysiological and neuroanatomical constraints (Pascual-Marqui, 2002).The accuracy of the sLORETA approach has been validated repeatedly from studies comparing sLORETA with other 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). Additionally, previous studies using sLORETA have proved accurate localization of deep brain structures such as the ACC (Pizzagalli et al., 2001) and the mesial temporal lobe (Zumsteg et al., 2006). We identified the cortical sources that generated the activity recorded by the scalp electrodes in each of the following eight frequency bands: delta (2–3.5 Hz), theta (4–7.5 Hz), alpha 1 (8–10 Hz), alpha 2 (10–12 Hz), beta 1 (13–18 Hz),

beta 2 (18.5–21 Hz), beta 3 (21.5–30 Hz), and gamma (30.5–44 Hz) (Lee et al., 2019). sLORETA computes electric neuronal activity as current density (A/m^2) without assuming a predefined number of active sources; its solution space consists of 6,239 voxels (5 mm × 5 mm × 5 mm) and is restricted to the cortical gray matter and hippocampus, as defined by the digitized Montreal Neurological Institute (MNI) (Fuchs et al., 2002) template 152. Scalp electrode coordinates on the MNI brain were derived from the International 5% System (Jurcak et al., 2007). In this study, statistical non-parametric mapping (SnPM), as introduced by Nichols and Holmes (Nichols et al., 2002), was adapted for permutation tests for source localization and functional connectivity analyses. It has been understood that sLORETA built-in voxel-wise randomization tests (5,000 permutations for voxel and frequency band) current density values can compute the averaged intracerebral current density distribution at time intervals exhibiting significant differences in non-parametric voxel-by-voxel one-tailored paired samples t-test on the three-dimensional sLORETA images. To display between-group differences in resting-state cortical oscillatory activities, sLORETA built-in voxel-wise randomization tests (5,000 permutations) were used to perform nonparametric statistical analyses of functional images with a threshold $P < 0.05$. The 5,000 random permutations were performed with correction for multiple testing (i.e., for tests performed for all electrodes and/or voxels and for all time samples and/or different frequencies); thus, further correction for multiple comparisons was unnecessary. Anatomical labeling of significant clusters was performed automatically using a sLORETA built-in toolbox. The locations of significant clusters were initially investigated using the Anatomy toolbox and reconfirmed using the Talairach and Tournoux atlas (Talairach et al., 1988).

2.5. Functional connectivity analysis

Dynamic functional connectivity between two brain regions has been estimated according to similarity and linear dependence (coherence) and nonlinear dependence (phase synchronization) between time-varying signals recorded in the two regions (Worsley et al., 2005). However, an instantaneous, non-physiological contribution caused by volume conduction and low spatial resolution can affect measures of dependence (Pascual-Marqui, 2007a). To overcome this limitation, a specialized technique (i.e., Hermitian covariance matrices) that removes this confounding factor has been suggested (Pascual-Marqui, 2007b). Measures of linear dependence (coherence) and nonlinear dependence (phase synchronization) between any number of multivariate time series are defined. These measures are calculated as sums of lagged and instantaneous dependences; they are non-negative, take the value zero only when there is pertinent independence, and are defined in the frequency domains as described above. Coherence and phase synchronization are interpreted as "connectivity" between locations. In this study, we selected a total of 16 regions of interest as functional nodes for functional connectivity analyses; the regions of interest were defined by their respective Brodmann areas (BAs) to be related to tinnitus perception according to previous studies. These nodes included the bilateral primary auditory cortices (BA 41 and 42) (Kringelbach, 2005; Rolls, 2004; Smits et al., 2007), bilateral parahippocampal gyri (BA 27) (Landgrebe et al., 2009; Song et al., 2015b), the bilateral dorsal (BA 24)/pregenual (BA 32)/subgenual anterior cingulate cortices (BA 25) (Damasio, 1996; De Ridder et al., 2011a; Song et al., 2015a; Song et al., 2016; Vanneste et al., 2010), the bilateral orbitofrontal cortices (BA 10) (Song et al., 2015b), and the bilateral inferior parietal lobule (BA 40) (Chen et al., 2018b; Houdayer et al., 2015).

Table 1
Demographics and clinical characteristics

	HL-NT group (N=65)	HL-T group (N=65)	*P* value
Age			
Mean (SD)	68.51±12.12	63.43±11.77	0.016*
range	19-88	15-85	
Sex			
male	34	39	0.380
female	31	26	
Laterality			
right	N/A	13 (20.0%)	NA
left		18 (27.7%)	
both		34 (52.3%)	
Character			
pure tone	N/A	43 (66.2%)	NA
narrow broad band		15 (23.1%)	
not determined		7 (10.8%)	
Mean hearing threshold[a]			
right ear (mean, SD)	45.17±8.83	43.94±9.72	0.85
left ear (mean, SD)	46.06±11.13	47.25±12.54	0.88
THI score[b]			
Median	NA	12	NA
range		2-16	

Abbreviation: HL-NT, hearing loss without tinnitus; HL-T, hearing loss with tinnitus; SD, standard deviation; HL, hearing loss; THI, tinnitus handicap inventory; NA, not available

* indicates statistical significance.

[a] Note that the mean hearing threshold was calculated using the average of the hearing thresholds at 0.5, 1, 2, and 4 kHz.

[b] Note that the THI score in HL-T group was not compatible with normal distribution.

2.6. Statistical analyses

Statistical non-parametric mapping (SnPM) was adapted for permutation tests for source localization and functional connectivity analyses. To identify between-group differences in resting-state cortical oscillatory activities, we used sLORETA built-in voxel-wise randomization tests (5,000 permutations for voxel and frequency band) to perform nonparametric statistical analyses of functional images. We also employed a between-groups *t*-statistic. Correction for multiple comparisons in SnPM using random permutations has shown to yield results similar to those obtained from a statistical parametric mapping approach using a general linear model with multiple comparison corrections (Nichols et al., 2002). For lagged linear connectivity differences, we compared between-group differences for each contrast using a paired-*t* statistic. We also corrected for multiple comparisons using LORETA-KEY built-in voxel-wise randomization tests for all voxels included in the 16 regions of interests for connectivity analyses (5,000 permutations). All analyses were performed and visualized using the R statistical software (ver. 3.3.2, R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-tailed, and significant differences were evaluated at a level of $P < 0.05$.

3. Results

3.1. Demographics and clinical characteristics

The demographics and clinical characteristics of the two groups are summarized in **Table 1**. An examination of the tinnitus laterality of the HL-T group showed that bilateral involvement was predominant, observed in 34 (52.3%) of the 65 subjects, followed by left (N = 18, 27.7%) and right (N = 13, 20.0%) unilateral tinnitus subjects. The most frequent psychoacoustic characteristics of tinnitus was pure tone (N = 43, 66.2%), followed by narrow band noise (N = 15, 23.1%). All included subjects met the THI criteria

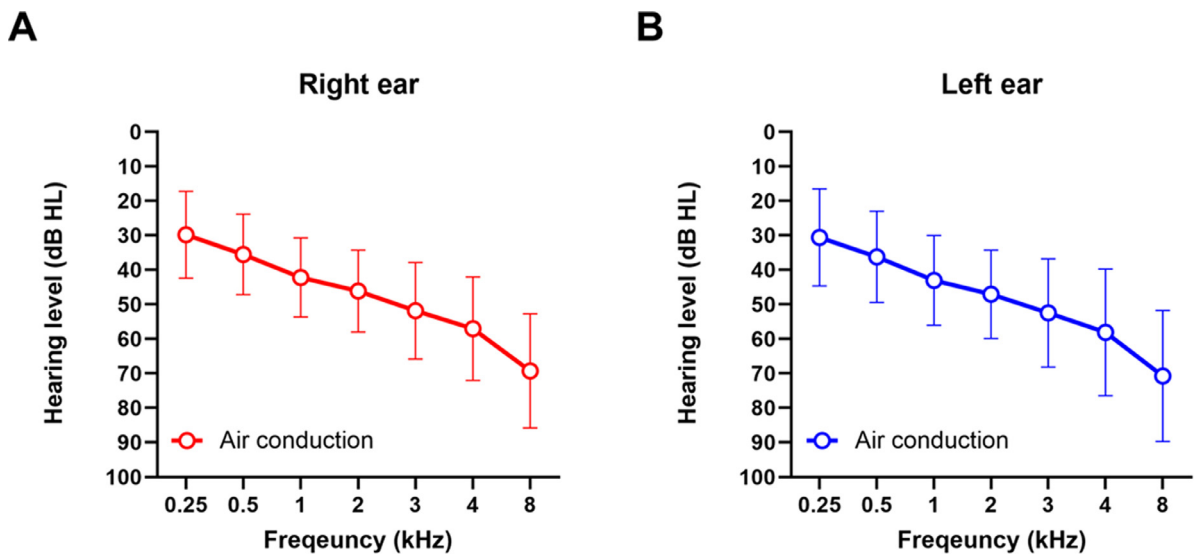

Figure 2. Audiological profile of cohorts included in the present study. Matched hearing thresholds across all frequencies (0.25–8 kHz) between the HL-T and HL-NT groups. The audiogram shows means ± standard deviation.

described above (<16), with a median THI score of 12 (range, 2–16). As shown in **Fig. 2**, hearing thresholds were matched across all frequencies between the two groups.

3.2. Source localization analyses

Compared to the HL-NT group, the HL-T group showed significantly higher activity in the right parahippocampus for the beta 1 frequency band ($P = 0.03$), in the left inferior parietal lobule (IPL) for the beta 2 frequency band ($P = 0.03$), and in the right IPL for the beta 3 and gamma frequency bands ($P = 0.04$) (**Fig. 3**). For all three areas that were found to be significantly different between the HL-T and H-NT groups, we have calculated the mean log-transformed current densities for the HL-T and H-NT groups and plotted in Figure 4. Meanwhile, no significant effects were observed for the delta, theta, alpha 1, or alpha 2 frequency bands.

3.3. Functional connectivity analyses

Compared to the HL-NT group, the HL-T group showed significantly higher functional connectivity between both parahippocampal gyri and the right IPL for the delta frequency band, and between the left posterior cingulate cortex (PCC) and right IPL for the beta 2 frequency band (P = 0.03) (**Fig. 5**). No significant between-group differences were found with regard to functional connectivity in the other six frequency bands.

4. Discussion

Disorders of consciousness are traditionally dealing with decreased consciousness. Yet, perceiving pain or sound in the absence of a corresponding stimulus may also be considered disorders of consciousness; rather, tinnitus raises tinnitus as a problem of hyperconsciousness. Thus, it is easily conceivable that the neural mechanisms of decreased consciousness (or unconsciousness) could benefit the understanding of hyperconsciousness underlying diverse neurological disorders, including tinnitus.

Consciousness requires thalamocortical activity (Akeju et al., 2014); specifically, thalamocortical dysrhythmia is a model proposed to explain tinnitus. Recent studies posited that altered DMN and thalamo-cortical functional connectivity are causally related to unconsciousness (Akeju et al., 2014), This echoes Merleau-Ponty's stance (Merleau-Ponty, 1945) involved in understanding self and others that everything that one is conscious-off needs to be related to the self and needs to be seen in its context. However, it also states that one can only be conscious of something one attends to, which can be top-down (selective attention) or bottom-up (perceptive attention). This is in agreement with the attention theory of conscious (awareness) (Graziano et al., 2011). Herein, understanding of the awareness would be verified through the current findings demonstrating that activation of the "circuit breaker" system and its functional connection to the parahippocampal tinnitus generator renders tinnitus as a salient event (see Discussion 4.3 section).

In this study we identified cortical oscillatory signatures for the selective development of tinnitus among subjects with HL by comparing rs-qEEG data between the HL-T and HL-NT groups. Our results showed that the HL-T group had significantly increased activity in the parahippocampal gyrus for the beta 1 frequency band and in the IPL for the beta 2, beta 3, and gamma frequency bands, compared to the HL-NT group. Our lagged linear functional connectivity analyses further demonstrated significantly higher connectivity between both parahippocampal gyri and the right IPL for the delta frequency band, and between the left PCC and the right IPL for the beta 2 frequency band in the HL-T group than in the HL-NT group. These findings are in keeping with the neural correlates of consciousness, in that both the parahippocampus, the PCC and IPL are part of the DMN and the IPL is also involved in attentional processing. Moreover, these results also are in agreement with the recently proposed Bayesian model and suggest that seminal neural substrates are involved in the selective development of tinnitus among subjects with HL.

4.1. Bayes and a model of the world

One of the main and central components of Bayes theorem is that priors are used to predict what sensory stimuli one expects in the world. Priors are based on a model of the world. These models of the world are also called cognitive maps, and are not limited to the spatial domain, but also include the auditory environment (Behrens et al., 2018) and can be regarded as extensions of simple tonotopic maps.

The parahippocampal gyrus is involved in auditory memory and thus may also play a role in tinnitus generation in subjects with HL

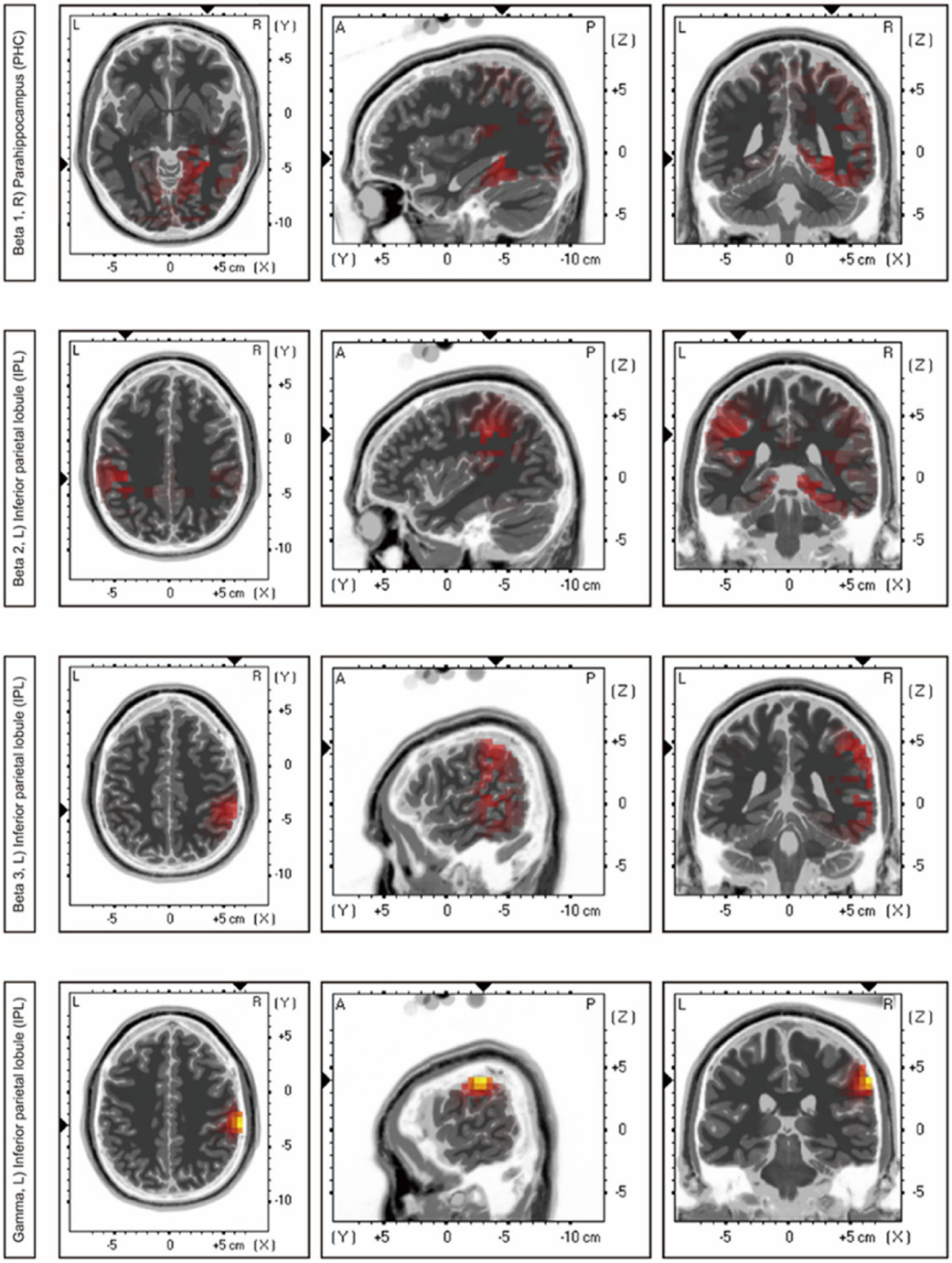

Figure 3. Standardized low-resolution brain electromagnetic tomography (sLORETA) source maps showing higher activity in the HL-T group than in the HL-NT group. Color intensity indicates the intensity of the signal contributing to the selective development of tinnitus among subjects with hearing loss.

(De Ridder et al., 2011b; De Ridder et al., 2006). Indeed, parahippocampal activity was increased in tinnitus subjects compared to non-tinnitus controls in a recent connectomics study (Mohan et al., 2016). Furthermore, a recent study that explored the effects of partial peripheral reafferentation via the use of hearing aids in tinnitus subjects showed that pre-hearing aid parahippocampal activity was a negative prognostic factor for tinnitus improvement (Han et al., 2020a).

Previous human and other animal studies have demonstrated that auditory deafferentation results in tinnitus generation only if precedent auditory memory exists (Eggermont et al., 2016; Lee et al., 2020a; Lee et al., 2020c; Lee et al., 2017). The Bayesian brain model states that the brain attempts to overcome missing auditory information by eliciting predictions via increases in topographically restricted tones, widening receptive fields, and rewiring dendrites and axons (De Ridder et al., 2014b). Importantly, if the uncertainty is not sufficiently compensated by neural plasticity or tonotopic reorganization within the auditory cortex, then missing auditory information may be retrieved from existing auditory memories stored in the parahippocampal gyrus (De Ridder et al., 2014b; Vanneste et al., 2016). In accordance with this theoretical model, the degree of missing auditory information, such as the severity and range of hearing loss, was shown to correlate with cortical oscillatory changes over the parahippocampal region in

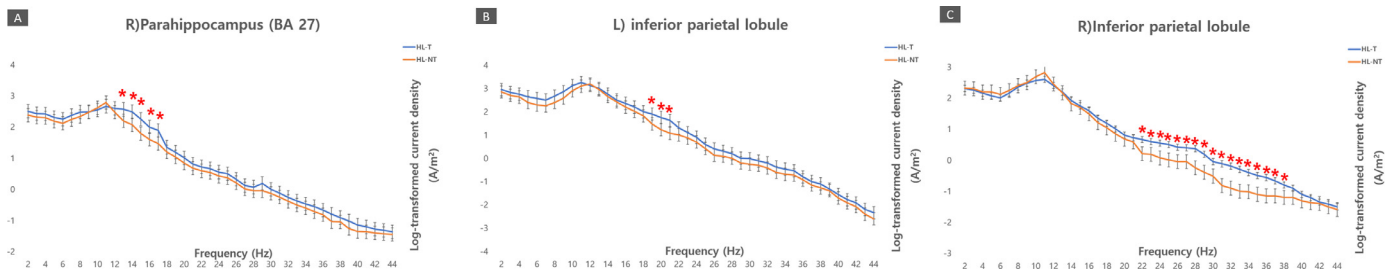

Figure 4. Comparisons of the power spectrum of the HL-T and HL-NT groups with regard to the right parahippocampus (A), left inferior parietal lobule (IPL) (B), and right IPL (C). Black whiskers indicate standard errors and asterisks denote frequencies that showed significant differences between the two groups. As in Figure 3, the HL-T group showed significantly higher mean log-transformed current density as compared with the HL-NT group for beta 1 frequency band of the right parahippocampus, beta 2 frequency band for the left IPL, and beta 3 and gamma frequency bands for the right IPL. R), right; L), left.

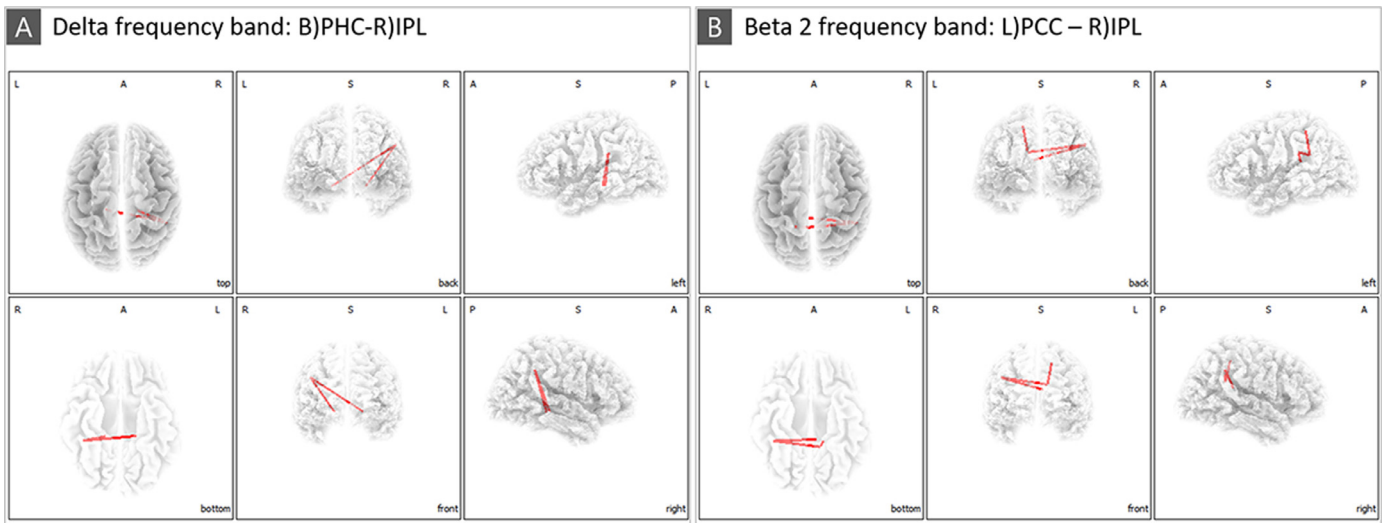

Figure 5. Functional connectivity analyses indicating cortical regions with significantly higher delta and beta 2 lagged phase synchronization in the HL-T group than in the HL-NT group. Delta lagged phase synchronization was significantly higher between both parahippocampal gyri and the right inferior parietal lobule (IPL), and beta 2 one was significantly higher between the left posterior cingulate cortex (PCC) and right IPL.

whole-brain analysis (Vanneste et al., 2016). Our results revealing higher source-localized activity in the parahippocampal gyrus in the HL-T group than in the HL-NT group (**Fig. 3A**), which are consistent with the recently proposed Bayesian brain model of tinnitus generation, support the notion that the parahippocampal gyrus is the primary generator of tinnitus in subjects with HL.

4.2. Activation of the "circuit breaker" system and its functional connection to the parahippocampal tinnitus generator renders tinnitus as a salient event

Selective attention refers to the ability to attend selectively to a particular salient object that is behaviorally relevant to a task while ignoring irrelevant information (Alain et al., 2000). Selective attention may be associated with endogenous attention, stimulus-driven attention, or a combination of both (Cabeza et al., 2008a; Corbetta et al., 2002; Sestieri et al., 2017). Endogenous attention is referred to as goal-driven attention (top-down), whereas stimulus-driven attention is referred to as exogenous attention (bottom-up), being driven by competition between sensory inputs (Cabeza et al., 2008a; Corbetta et al., 2002; Sestieri et al., 2017). Previous neuroimaging studies have consistently documented the contribution of a bilateral network of the frontoparietal regions to selective attention (Chun et al., 2011; Wiegand et al., 2018). Such stimulus-driven attention is driven by a ventral attention system comprising regions of the IPL; this system captures attention in a bottom-up fashion (Corbetta et al., 2002). When unexpected stimuli such as auditory phantom percepts are presented, this network reorients the attentional set that acts as a "circuit breaker" for the dorsal attention system, subserving a top-down orientation as it disengages preexisting attention and subsequently directs attentional resources to salient events (Corbetta et al., 2002). Indeed, previous studies have demonstrated that the IPL contributes to deficits of attentional disengagement, suggesting that the mechanism to disengage is a prerequisite for selective attention (Corbetta et al., 2005; Vossel et al., 2006). Notably, the ventral attention network appears to be involved in both stimulus-driven attention and sustained attention (Rosenberg et al., 2016). In the current study, we observed higher source-localized activity of the left IPL for the beta 2 frequency band and the right IPL for the beta 3 and gamma frequency bands in the HL-T group than in the HL-NT group (**Fig. 3**), which may indicate that the activated circuit breaker system renders tinnitus as a salient event in the milieu of decreased peripheral auditory input. This system may continue to perceive tinnitus as a salient event thereafter.

Functional connectivity analyses also demonstrated that the HL-T group manifested significantly higher resting-state connectivity between the IPL and the parahippocampus than the HL-NT group for the delta frequency band (**Fig. 5A**). A recent study suggested that the inferior parietal areas are linked to auditory memory and awareness, and thus serve as a core region in the tinnitus network (Paraskevopoulos et al., 2019). Other studies have also proposed that the inferior parietal area may attribute tinnitus to an external source, such that it may originate from the parahippocam-

pus (De Ridder et al., 2014c). Based on the findings of these studies, which are consistent with our results, we surmise that tinnitus generation due to parahippocampus-based Bayesian updating is actively linked to the IPL, and thus was saliently perceived in the HL-T group.

The IPL has been linked to Bayesian updating from memory (d'Acremont et al., 2013). Therefore, if the sensory system cannot provide sufficient evidence to support prior beliefs, the brain will resort to memory to update the prior beliefs (De Ridder et al., 2014a), and will then extract the most recent memory associated with the same stimulus in the same context.

4.3. In subjects with HL, tinnitus may be regarded as a norm when the circuit breaker system is actively linked to the default mode network

We observed increased resting-state functional connectivity between the right IPL and left PCC in the HL-T group compared to the HL-NT group (**Fig. 5B**). The PCC is a core component of the DMN. The DMN represents a distributed functional-anatomic network exhibiting a high rate of metabolism in subjects not focused on the outside world, and decreased activity across a range of cognitive loads (Kim, 2010; Raichle et al., 2001; Shulman et al., 1997). It is considered a self-representational network, encoding the self within an environment or context (Andrews-Hanna et al., 2010; Buckner et al., 2008; Raichle, 2015). Previous studies have reported that the PCC is involved in detecting sensory changes and drives subsequent shifts in self-referential processing and thus behavior based on Bayesian inference (Pearson et al., 2011). It furthermore encodes the relation of the self in the environment (Leech et al., 2013), including the auditory environment.

Importantly, the task-negative mode may not be deactivated during conscious perception of tinnitus. In lieu of DMN deactivation, tinnitus generators may become integrated with the DMN in patients with tinnitus (Vanneste et al., 2012a). This could suggest that the tinnitus has become the default state, the norm. Indeed, recent studies have shown that tinnitus perception and distress are positively correlated with increased resting-state functional connectivity between core regions within the DMN (Chen et al., 2018a; Schmidt et al., 2013a), and resting-state EEG data have shown that PCC activation is critical in both pure tone and narrowband noise tinnitus, as well as tinnitus-related distress (Vanneste et al., 2012a).

Previous studies have indicated that functional connectivity between subregions of the IPL and PCC are closely associated with cognitive deficits (Wang et al., 2015; Zhang et al., 2014). Although there have been contradictory reports of the effects of tinnitus on cognitive function or speech perception (Lee et al., 2020b; Zeng et al., 2020), the role of the functional connection between the IPL and PCC remains largely unknown in the context of tinnitus perception. Given that the increased resting-state functional connectivity between the PCC and the parahippocampus have already been revealed in subjects with tinnitus (Husain et al., 2014; Vanneste et al., 2012a), the IPL may act as a connecting node between the parahippocampus and the PCC. Overall, subjects with HL may perceive tinnitus when auditory memory-based phantom sound generated in the parahippocampus is connected to the IPL-based circuit breaker system, and the circuit breaker signal is then connected to the PCC-based DMN to render the auditory phantom as a norm (**Fig. 6**). This is in keeping with the concept that the IPL attaches attention to medial temporal lobe memory (hippocampus and parahippocampus) and thereby pushes memory based percepts to consciousness (Cabeza et al., 2008b; Cabeza et al., 2011), in agreement with a previously posited hypothesis of the tinnitus core, which includes the auditory cortex, parahippocampus, inferior parietal area (and possibly ventrolateral prefrontal cortex) (De Ridder et al., 2014c).

4.4. Strengths and limitations of this study

The present study replicated previous findings of functional neuroimaging studies in tinnitus subjects and identified crucial cortical changes that may be responsible for the selective development of tinnitus in subjects with HL. The major strength of this study is that we matched hearing thresholds throughout all frequencies between the HL-T and HL-NT groups and minimized bias related to distress-induced cortical changes by recruiting only minimally distressed tinnitus subjects for the HL-T group. Our results strongly indicate that parahippocampal auditory memory, the circuit breaker system, and the default mode network are involved in the selective development of tinnitus among subjects with HL. Considering that transcranial magnetic stimulation over the parietal areas including the IPL can modulate the perception of tinnitus and its distress, the clinical implication of the present study may include a possibility of tailored application of neuromodulatory treatment particularly insubsequent tinnitus distress (Vanneste et al., 2012b), the clinical implications of the present study may include the possibility of tailored application of neuromodulatory treatment, particularly among tinnitus subjects with HL. Also, according to recent studies, cortical activity changes in the parahippocampus and IFG may serve as the neural mechanism underlying the effects of therapeutics on tinnitus. For instance, recent studies have revealed that sound therapy markedly attenuated tinnitus by altering functional activity involving the left parahippocampal gyrus (Han et al., 2020b) as well as enhancing the tinnitus-canceling system, including IFG (Han et al., 2019). In this regard, the current findings would provide insights on the neural correlates-based tailored therapeutics for tinnitus relief, particularly among tinnitus subjects with hearing loss.

Nevertheless, this study had some limitations that should be addressed in future follow-up studies. First, the hearing levels of subjects with tinnitus were evaluated using a standard PTA that was limited to 8,000 Hz. However, previous literature have shown that tinnitus can occur in subjects with slight HL at ultra-high frequencies (>8000 Hz) (Melcher et al., 2013). Therefore, future follow-up studies matching hearing thresholds up to ultra-high frequencies between groups should be performed to evaluate the replicability of the current study. Second, although we attempted to minimize the bias associated with the amount of HL and distress-induced cortical changes, our results may still be inconclusive when considering additional potential confounders such as the etiology or the duration of HL (Vanneste et al., 2018b; Vanneste et al., 2011). In particular, we could not match average age between the HL-T and HL-NT groups. Because the onset age of tinnitus may affect cortical oscillatory patterns, according to our own previous study (Song et al., 2013), future follow-up studies matched for all possible demographic characteristics are warranted. Third, adding a negative control group with normal hearing thresholds and no tinnitus to the current study group may offer us further insights about the selective development of tinnitus in subjects with HL (Husain et al., 2011; Schmidt et al., 2013b). Future studies including a negative control group and comparing this group to HL with- or without tinnitus groups are warranted. Forth, an intra-group study exploring the cortical oscillatory patterns before and after improvements in tinnitus symptoms may provide additional support for understanding the selective development of tinnitus in subjects with HL. Future studies applying various treatment options (Eggermont, 2012; Langguth et al., 2013) and compare and comparing pre- and post-tinnitus improvement cortical oscillatory patterns would be useful for studying tinnitus-related neural substrates and validating the current results. Fifth, the current results with the IPL emerging as a significant area in tinnitus subjects in different frequency bands and different laterality might have biased by inherent low resolution of qEEG and

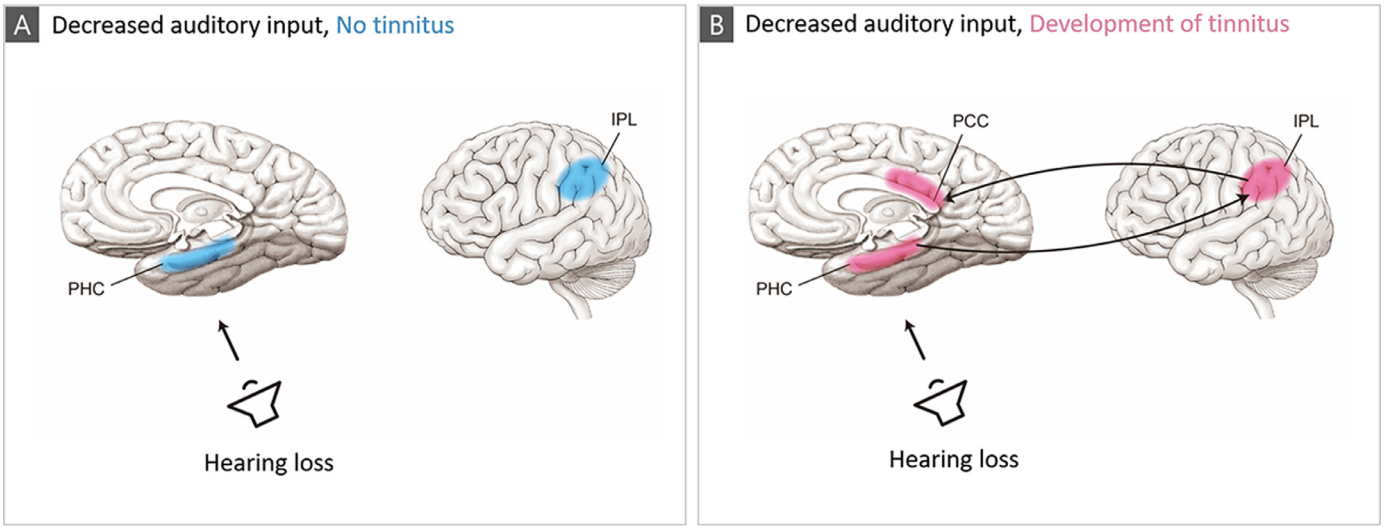

Figure 6. Schematic illustration of the neurobiological mechanism of selective tinnitus development in subjects with hearing loss.

limited numbers of study subjects. Future follow-up studies using other functional imaging methodologies and a larger number of subjects should be performed to check the replicability of the current study. Finally, although the permutation approach used in the current study has been designed to guard against the increased comparisons due to the number of voxels, repeated use of multiple t-tests on multiple maps may increase false-positive rate. Further studies using different statistical approaches should be performed to evaluate the reproducibility of the current results.

5. Conclusion

Taken together, our results suggest that peripheral HL-evoked tinnitus may be perceived only if auditory memory stored in the parahippocampus is actively linked to the IPL-based circuit breaker system and the circuit breaker signal is connected to the PCC-based DMN. Thus, when the circuit breaker system regards tinnitus secondary to peripheral deafferentation as a salient event and the DMN regards tinnitus as a norm, subjects with HL may consciously perceive tinnitus. Collectively, our results further refine the recently proposed Bayesian model and decipher the neurobiological mechanism of the selective development of tinnitus in subjects with HL.

Author contributions

SYL, MYC, and JJS led the analysis and interpretation of the results, and drafted the first manuscript. BYC, JWK, and DR conceived the investigation, revised the manuscript for important intellectual content. All authors contributed to all aspects of the investigation, including methodological design, data collection and analysis, interpretation of the results, and revision of the manuscript for important intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

CRediT authorship contribution statement

Sang-Yeon Lee: Formal analysis, Writing – original draft. **Munyoung Chang:** Writing – original draft. **Byungjoon Kwon:** Formal analysis. **Byung Yoon Choi:** Writing – review & editing. **Ja-Won Koo:** Writing – review & editing. **Taesup Moon:** Formal analysis. **Dirk De Ridder:** Writing – original draft. **Sven Vanneste:** Writing – review & editing. **Jae-Jin Song:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing.

Funding

This work was supported by grants from the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (grant No. NRF-2019R1A2C2004941) and from Seoul National University Bundang Hospital (grant No. 13-2017-007).

Acknowledgments

The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: http://www.textcheck.com/certificate/8QiQBI

References

Akeju, O., Loggia, M.L., Catana, C., Pavone, K.J., Vazquez, R., Rhee, J., Contreras Ramirez, V., Chonde, D.B., Izquierdo-Garcia, D., Arabasz, G., Hsu, S., Habeeb, K., Hooker, J.M., Napadow, V., Brown, E.N., Purdon, P.L., 2014. Disruption of thalamic functional connectivity is a neural correlate of dexmedetomidine-induced unconsciousness. Elife 3, e04499.
Alain, C., Arnott, S.R, 2000. Selectively attending to auditory objects. Front. Biosci 5, D202–D212.
Andrews-Hanna, J.R., Reidler, J.S., Sepulcre, J., Poulin, R., Buckner, R.L, 2010. Functional-anatomic fractionation of the brain's default network. Neuron 65, 550–562.
Behrens, T.E.J., Muller, T.H., Whittington, J.C.R., Mark, S., Baram, A.B., Stachenfeld, K.L., Kurth-Nelson, Z., 2018. What Is a Cognitive Map? Organizing Knowledge for Flexible Behavior. Neuron 100, 490–509.
Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L, 2008. The brain's default network: anatomy, function, and relevance to disease. Ann N Y Acad. Sci 1124, 1–38.
Cabeza, R., Ciaramelli, E., Olson, I.R., Moscovitch, M., 2008a. The parietal cortex and episodic memory: an attentional account. Nature Rev. Neurosci. 9, 613–625.
Cabeza, R., Ciaramelli, E., Olson, I.R., Moscovitch, M., 2008b. The parietal cortex and episodic memory: an attentional account. Nat. Rev. Neurosci. 9, 613–625.
Cabeza, R., Mazuz, Y.S., Stokes, J., Kragel, J.E., Woldorff, M.G., Ciaramelli, E., Olson, I.R., Moscovitch, M., 2011. Overlapping parietal activity in memory and perception: evidence for the attention to memory model. J. Cogn. Neurosci. 23, 3209–3217.
Chen, Y.-C., Chen, H., Bo, F., Xu, J.-J., Deng, Y., Lv, H., Cai, Y., Xia, W., Yin, X., Gu, J.-P., 2018a. Tinnitus distress is associated with enhanced resting-state functional

connectivity within the default mode network. Neuropsychiatric Dis. Treat. 14, 1919.
Chen, Y.C., Xia, W., Chen, H., Feng, Y., Xu, J.J., Gu, J.P., Salvi, R., Yin, X., 2017. Tinnitus distress is linked to enhanced resting-state functional connectivity from the limbic system to the auditory cortex. Human Brain Mapp. 38, 2384–2397.
Chen, Y.C., Liu, S., Lv, H., Bo, F., Feng, Y., Chen, H., Xu, J.J., Yin, X., Wang, S., Gu, J.P, 2018b. Abnormal resting-state functional connectivity of the anterior cingulate cortex in unilateral chronic tinnitus patients. Front. Neurosci. 12, 9.
Chun, M.M., Golomb, J.D., Turk-Browne, N.B., 2011. A taxonomy of external and internal attention. Ann. Rev. Psychol. 62, 73–101.
Corbetta, M., Shulman, G.L, 2002. Control of goal-directed and stimulus-driven attention in the brain. Nature Rev. Neurosci. 3, 201–215.
Corbetta, M., Kincade, M.J., Lewis, C., Snyder, A.Z., Sapir, A., 2005. Neural basis and recovery of spatial attention deficits in spatial neglect. Nature Neurosci. 8, 1603–1610.
d'Acremont, M., Schultz, W., Bossaerts, P., 2013. The human brain encodes event frequencies while forming subjective beliefs. J. Neurosci. 33, 10887–10897.
Damasio, A.R., 1996. The somatic marker hypothesis and the possible functions of the prefrontal cortex. Philos Trans. R. Soc. Lond. Ser. B, Biol. Sci. 351, 1413–1420.
De Ridder, D., Vanneste, S., Congedo, M., 2011a. The distressed brain: a group blind source separation analysis on tinnitus. PLoS One 6, e24273.
De Ridder, D., Vanneste, S., Freeman, W., 2014a. The Bayesian brain: Phantom percepts resolve sensory uncertainty. Neurosci. Biobehav. Rev. 44C, 4–15.
De Ridder, D., Vanneste, S., Freeman, W., 2014b. The Bayesian brain: phantom percepts resolve sensory uncertainty. Neurosci. Biobehav. Rev. 44, 4–15.
De Ridder, D., Elgoyhen, A.B., Romo, R., Langguth, B., 2011b. Phantom percepts: tinnitus and pain as persisting aversive memory networks. Proc. Natl. Acad. Sci. U.S.A. 108, 8075–8080.
De Ridder, D., Fransen, H., Francois, O., Sunaert, S., Kovacs, S., Van De Heyning, P., 2006. Amygdalohippocampal involvement in tinnitus and auditory memory. Acta Otolaryngol. Suppl. 50–53.
De Ridder, D., Vanneste, S., Weisz, N., Londero, A., Schlee, W., Elgoyhen, A.B., Langguth, B., 2014c. An integrative model of auditory phantom perception: tinnitus as a unified percept of interacting separable subnetworks. Neurosci. Biobehav. Rev. 44, 16–32.
Dierks, T., Jelic, V., Pascual-Marqui, R.D., Wahlund, L., Julin, P., Linden, D.E., 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.
Eggermont, J.J., 2012. The neuroscience of tinnitus. Oxford University Press.
Eggermont, J.J., Kral, A., 2016. Somatic memory and gain increase as preconditions for tinnitus: Insights from congenital deafness. Hear. Res. 333, 37–48.
Fuchs, M., Kastner, J., Wagner, M., Hawes, S., Ebersole, J.S, 2002. A standardized boundary element method volume conductor model. Clin. Neurophysiol. 113, 702–712.
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.
Graziano, M.S., Kastner, S., 2011. Human consciousness and its relationship to social neuroscience: A novel hypothesis. Cognit. Neurosci. 2, 98–113.
Han, J.J., Jang, J.H., Ridder, D., Vanneste, S., Koo, J.W., Song, J.J, 2018. Increased parietal circuit-breaker activity in delta frequency band and abnormal delta/theta band connectivity in salience network in hyperacusis subjects. PLoS One 13, e0191858.
Han, J.J., Ridder, D., Vanneste, S., Chen, Y.C., Koo, J.W., Song, J.J., 2020a. Pre-treatment ongoing cortical oscillatory activity predicts improvement of tinnitus after partial peripheral reafferentation with hearing Aids. Front. Neurosci. 14, 410.
Han, L., Pengfei, Z., Chunli, L., Zhaodi, W., Xindi, W., Qian, C., Shusheng, G., Zhenchang, W., 2020b. The effects of sound therapy in tinnitus are characterized by altered limbic and auditory networks. Brain Commun. 2, fcaa131.
Han, S.A., Choe, G., Kim, Y., Koo, J.W., Choi, B.Y., Song, J.J, 2019. Beware of a fragile footplate: lessons from ossiculoplasty in patients with ossicular anomalies related to second pharyngeal arch defects. J. Clin. Med. 8.
Houdayer, E., Teggi, R., Velikova, S., Gonzalez-Rosa, J.J., Bussi, M., Comi, G., Leocani, L., 2015. Involvement of cortico-subcortical circuits in normoacousic chronic tinnitus: A source localization EEG study. Clin. Neurophysiol. 126, 2356–2365.
Huh, G., Bae, Y.J., Woo, H.J., Park, J.H., Koo, J.W., Song, J.J, 2020. Vestibulocochlear symptoms caused by vertebrobasilar dolichoectasia. Clin. Exp. Otorhinolaryngol. 13, 123–132.
Husain, F.T., Schmidt, S.A, 2014. Using resting state functional connectivity to unravel networks of tinnitus. Hear. Res. 307, 153–162.
Husain, F.T., Pajor, N.M., Smith, J.F., Kim, H.J., Rudy, S., Zalewski, C., Brewer, C., Horwitz, B., 2011. Discrimination task reveals differences in neural bases of tinnitus and hearing impairment. PLoS One 6, e26639.
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.
Kim, H., 2010. Dissociating the roles of the default-mode, dorsal, and ventral networks in episodic memory retrieval. Neuroimage 50, 1648–1657.
Koprivova, J., Congedo, M., Horacek, J., Prasko, J., Raszka, M., Brunovsky, M., Kohutova, B., Hoschl, C., 2011. EEG source analysis in obsessive-compulsive disorder. Clinical Neurophysiol. : off. J. Int. Federat. Clin. Neurophysiol. 122, 1735–1743.
Korucuoglu, O., Gladwin, T.E., Wiers, R.W, 2016. The effect of acute alcohol on motor-related EEG asymmetries during preparation of approach or avoid alcohol responses. Biol. Psychol. 114, 81–92.
Kringelbach, M.L., 2005. The human orbitofrontal cortex: linking reward to hedonic experience. Nature Rev. Neurosci. 6, 691–702.
Lan, L., Li, J., Chen, Y., Chen, W., Li, W., Zhao, F., Chen, G., Liu, J., Chen, Y., Li, Y., Wang, C.D., Zheng, Y., Cai, Y., 2020. Alterations of brain activity and functional connectivity in transition from acute to chronic tinnitus. Human Brain Mapping.
Landgrebe, M., Langguth, B., Rosengarth, K., Braun, S., Koch, A., Kleinjung, T., May, A., de Ridder, D., Hajak, G., 2009. Structural brain changes in tinnitus: grey matter decrease in auditory and non-auditory brain areas. Neuroimage 46, 213–218.
Langguth, B., De Ridder, D., 2013. Tinnitus: therapeutic use of superficial brain stimulation. In: Handbook of Clinical Neurology. Elsevier, pp. 441–467 Vol. 116.
Lee, J.M., Kim, Y., Ji, J.-Y., Koo, J.-W., Song, J.-J., 2020a. Auditory experience, for a certain duration, is a prerequisite for tinnitus: lessons from subjects with unilateral tinnitus in the better-hearing ear. Progress in Brain Research. Elsevier.
Lee, S.-Y., Lee, J.Y., Han, S.-Y., Seo, Y., Shim, Y.J., Kim, Y.H, 2020b. Neurocognition of aged patients with chronic tinnitus: focus on mild cognitive impairment. Clin. Exp. Otorhinolaryngol. 13, 8.
Lee, S.Y., Choi, B.Y., Koo, J.W., De Ridder, D., Song, J.J, 2020c. Cortical oscillatory signatures reveal the prerequisites for tinnitus perception: a comparison of subjects with sudden sensorineural hearing loss with and without tinnitus. Front. Neurosci. 14, 596647.
Lee, S.Y., Nam, D.W., Koo, J.W., De Ridder, D., Vanneste, S., Song, J.J, 2017. No auditory experience, no tinnitus: lessons from subjects with congenital- and acquired single-sided deafness. Hear. Res. 354, 9–15.
Lee, S.Y., Rhee, J., Shim, Y.J., Kim, Y., Koo, J.W., De Ridder, D., Vanneste, S., Song, J.J, 2019. Changes in the resting-state cortical oscillatory activity 6 months after modified tinnitus retraining therapy. Front Neurosci 13, 1123.
Lee, S.Y., Kim, M.K., Bae, Y.J., An, G.S., Lee, K., Choi, B.Y., Koo, J.W., Song, J.J., 2020d. Longitudinal analysis of surgical outcome in subjects with pulsatile tinnitus originating from the sigmoid sinus. Sci. Rep. 10, 18194.
Leech, R., Sharp, D.J, 2013. The role of the posterior cingulate cortex in cognition and disease. Brain.
Melcher, J.R., Knudson, I.M., Levine, R.A, 2013. Subcallosal brain structure: correlation with hearing threshold at supra-clinical frequencies (>8 kHz), but not with tinnitus. Hear. Res. 295, 79–86.
Merleau-Ponty, M., 1945. Phénomènologie de la Perception, English edition ed. Gallimard, Paris.
Milner, R., Lewandowska, M., Ganc, M., Nikadon, J., Niedzialek, I., Jedrzejczak, W.W., Skarzynski, H., 2020. Electrophysiological correlates of focused attention on low- and high-distressed tinnitus. PLoS One 15, e0236521.
Mohan, A., De Ridder, D., Vanneste, S., 2016. Emerging hubs in phantom perception connectomics. Neuroimage Clin. 11, 181–194.
Mulert, C., Jager, L., Schmitt, R., Bussfeld, P., Pogarell, O., Moller, H.J., 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, T.E., Holmes, A.P, 2002. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum. Brain Mapp. 15, 1–25.
Norena, A., Micheyl, C., Chery-Croze, S., Collet, L., 2002. Psychoacoustic characterization of the tinnitus spectrum: implications for the underlying mechanisms of tinnitus. Audiol. Neurootol. 7, 358–369.
Paraskevopoulos, E., Dobel, C., Wollbrink, A., Salvari, V., Bamidis, P.D., Pantev, C., 2019. Maladaptive alterations of resting state cortical network in Tinnitus: a directed functional connectivity analysis of a larger MEG data set. Sci. Rep. 9, 1–11.
Pascual-Marqui, R.D., 2002. Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. Method. Find. Exp. Clin. Pharmacol. 24 (Suppl D), 5–12.
Pascual-Marqui, R.D. 2007a. Discrete, 3D distributed, linear imaging methods of electric neuronal activity. Part 1: exact, zero error localization. Arxiv preprint arXiv, 0710.3341.
Pascual-Marqui, R.D. 2007b. Instantaneous and lagged measurements of linear and nonlinear dependence between groups of multivariate time series: frequency decomposition. Arxiv preprint arXiv, 1455.
Pearson, J.M., Heilbronner, S.R., Barack, D.L., Hayden, B.Y., Platt, M.L, 2011. Posterior cingulate cortex: adapting behavior to a changing world. Trends Cogn. Sci. 15, 143–151.
Pinto, P., Marcelos, C., Mezzasalma, M., Osterne, F., de Lima, M.d.M.T., Nardi, A., 2014. Tinnitus and its association with psychiatric disorders: systematic review. J. Laryngol. Otol. 128, 660–664.
Pizzagalli, D., Pascual-Marqui, R.D., Nitschke, J.B., Oakes, T.R., Larson, C.L., Abercrombie, H.C., Schaefer, S.M., Koger, J.V., Benca, R.M., Davidson, R.J, 2001. Anterior cingulate activity as a predictor of degree of treatment response in major depression: evidence from brain electrical tomography analysis. A. J. Psychiatry 158, 405–415.
Pizzagalli, D.A., Oakes, T.R., Fox, A.S., Chung, M.K., Larson, C.L., Abercrombie, H.C., Schaefer, S.M., Benca, R.M., Davidson, R.J, 2004. Functional but not structural subgenual prefrontal cortex abnormalities in melancholia. Mol. Psychiatry 9 (325), 393–405.
Raichle, M.E., 2015. The brain's default mode network. Annu. Rev. Neurosci. 38, 433–447.
Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L, 2001. A default mode of brain function. Proc. Natl. Acad. Sci. U. S. A. 98, 676–682.

Rauschecker, J.P., Leaver, A.M., Mühlau, M., 2010. Tuning out the noise: limbic-auditory interactions in tinnitus. Neuron 66, 819–826.
Rolls, E.T., 2004. The functions of the orbitofrontal cortex. Brain Cognit. 55, 11–29.
Rosenberg, M.D., Finn, E.S., Scheinost, D., Papademetris, X., Shen, X., Constable, R.T., Chun, M.M, 2016. A neuromarker of sustained attention from whole-brain functional connectivity. Nature Neurosci. 19, 165.
Schecklmann, M., Vielsmeier, V., Steffens, T., Landgrebe, M., Langguth, B., Kleinjung, T., 2012. Relationship between audiometric slope and tinnitus pitch in tinnitus patients: insights into the mechanisms of tinnitus generation. PLoS One 7.
Schmidt, S.A., Akrofi, K., Carpenter-Thompson, J.R., Husain, F.T, 2013a. Default mode, dorsal attention and auditory resting state networks exhibit differential functional connectivity in tinnitus and hearing loss. PLoS One 8.
Schmidt, S.A., Akrofi, K., Carpenter-Thompson, J.R., Husain, F.T, 2013b. Default mode, dorsal attention and auditory resting state networks exhibit differential functional connectivity in tinnitus and hearing loss. PLoS One 8, e76488.
Sestieri, C., Shulman, G.L., Corbetta, M., 2017. The contribution of the human posterior parietal cortex to episodic memory. Nature Rev. Neurosci. 18, 183.
Sherlin, L., Congedo, M., 2005. Obsessive-compulsive dimension localized using low-resolution brain electromagnetic tomography (LORETA). Neurosci. Lett. 387, 72–74.
Shulman, G.L., Fiez, J.A., Corbetta, M., Buckner, R.L., Miezin, F.M., Raichle, M.E., Petersen, S.E, 1997. Common Blood Flow Changes across Visual Tasks: II. Decreases in Cerebral Cortex. J. Cogn. Neurosci. 9, 648–663.
Siepmann, M., Kirch, W., 2002. Effects of caffeine on topographic quantitative EEG. Neuropsychobiology 45, 161–166.
Smits, M., Kovacs, S., de Ridder, D., Peeters, R.R., van Hecke, P., Sunaert, S., 2007. Lateralization of functional magnetic resonance imaging (fMRI) activation in the auditory pathway of patients with lateralized tinnitus. Neuroradiology 49, 669–679.
Song, J.-J., De Ridder, D., Schlee, W., Van de Heyning, P., Vanneste, S., 2013. "Distressed aging": the differences in brain activity between early-and late-onset tinnitus. Neurobiol. Aging 34, 1853–1863.
Song, J.J., Vanneste, S., De Ridder, D., 2015a. Dysfunctional noise cancelling of the rostral anterior cingulate cortex in tinnitus patients. PLoS One 10, e0123538.
Song, J.J., Vanneste, S., Schlee, W., Van de Heyning, P., De Ridder, D., 2015b. 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. Brain Struct. Funct. 220, 571–584.
Song, J.J., An, G.S., Choi, I., De Ridder, D., Kim, S.Y., Choi, H.S., Park, J.H., Choi, B.Y., Koo, J.W., Lee, K., 2016. Objectification and differential diagnosis of vascular pulsatile tinnitus by transcanal sound recording and spectrotemporal analysis: a preliminary study. Otol. Neurotol. 37, 613–620.
Song, J.J., Kim, K., Sunwoo, W., Mertens, G., Van de Heyning, P., De Ridder, D., Vanneste, S., Lee, S.Y., Park, K.J., Choi, H., Choi, J.W, 2017. A Quantitative electroencephalography study on cochlear implant-induced cortical changes in single-sided deafness with tinnitus. Front Hum Neurosci 11, 210.
Souza, D.D.S., Almeida, A.A., Andrade, S., Machado, D., Leitao, M., Sanchez, T.G., Rosa, M., 2020. Transcranial direct current stimulation improves tinnitus perception and modulates cortical electrical activity in patients with tinnitus: A randomized clinical trial. Neurophysiol. Clin. 50, 289–300.
Talairach, J., Tornoux, P., 1988. Co-planar Stereotaxic Atlas of the Human Brain: 3-Dimensional Proportional System: An Approach to Cerebral Imaging. Georg Thieme, Stuttgart.
Tan, C.M., Lecluyse, W., McFerran, D., Meddis, R., 2013. Tinnitus and patterns of hearing loss. J. Assoc. Res. Otolaryngol. 14, 275–282.
Vanneste, S., De Ridder, D., 2012a. The auditory and non-auditory brain areas involved in tinnitus. An emergent property of multiple parallel overlapping subnetworks. Front. Syst. Neurosci. 6, 31.
Vanneste, S., De Ridder, D., 2016. Deafferentation-based pathophysiological differences in phantom sound: tinnitus with and without hearing loss. Neuroimage 129, 80–94.
Vanneste, S., Song, J.J., De Ridder, D., 2018a. Thalamocortical dysrhythmia detected by machine learning. Nat. Commun. 9, 1103.
Vanneste, S., Alsalman, O., De Ridder, D., 2018b. COMT and the neurogenetic architecture of hearing loss induced tinnitus. Hear. Res. 365, 1–15.
Vanneste, S., Alsalman, O., De Ridder, D., 2019. Top-down and bottom-up regulated auditory phantom perception. J. Neurosci. 39, 364–378.
Vanneste, S., van der Loo, E., Plazier, M., De Ridder, D., 2012b. Parietal double-cone coil stimulation in tinnitus. Experimental brain research 221, 337–343.
Vanneste, S., Plazier, M., van der Loo, E., Van de Heyning, P., De Ridder, D., 2011. The difference between uni-and bilateral auditory phantom percept. Clin. Neurophysiol. 122, 578–587.
Vanneste, S., Plazier, M., der Loo, E., de Heyning, P.V., Congedo, M., De Ridder, D., 2010. The neural correlates of tinnitus-related distress. Neuroimage 52, 470–480.
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.
Vossel, S., Thiel, C.M., Fink, G.R, 2006. Cue validity modulates the neural correlates of covert endogenous orienting of attention in parietal and frontal cortex. Neuroimage 32, 1257–1264.
Wang, Z., Xia, M., Dai, Z., Liang, X., Song, H., He, Y., Li, K., 2015. Differentially disrupted functional connectivity of the subregions of the inferior parietal lobule in Alzheimer's disease. Brain Struct. Funct. 220, 745–762.
White, D.J., Congedo, M., Ciorciari, J., Silberstein, R.B, 2012. Brain oscillatory activity during spatial navigation: theta and gamma activity link medial temporal and parietal regions. J. Cognit. Neurosci. 24, 686–697.
Wiegand, K., Heiland, S., Uhlig, C.H., Dykstra, A.R., Gutschalk, A., 2018. Cortical networks for auditory detection with and without informational masking: task effects and implications for conscious perception. Neuroimage 167, 178–190.
Worrell, G.A., Lagerlund, T.D., Sharbrough, F.W., Brinkmann, B.H., Busacker, N.E., Cicora, K.M., O'Brien, T.J., 2000. Localization of the epileptic focus by low-resolution electromagnetic tomography in patients with a lesion demonstrated by MRI. Brain Topogr. 12, 273–282.
Worsley, K.J., Chen, J.I., Lerch, J., Evans, A.C, 2005. Comparing functional connectivity via thresholding correlations and singular value decomposition. Philos. Trans. R. Soc. Lond.. Ser. B, Biol. Sci. 360, 913–920.
Zeng, F.G., Richardson, M., Turner, K., 2020. Tinnitus does not interfere with auditory and speech perception. J. Neurosci. 40, 6007–6017.
Zhang, J., Zhang, Z., Huang, S., Zhou, H., Feng, Y., Shi, H., Wang, D., Nan, W., Wang, H., Yin, S., 2020a. Differences in clinical characteristics and brain activity between patients with low- and high-frequency tinnitus. Neural Plast. 2020, 5285362.
Zhang, S., Li, C.-S.R., 2014. Functional clustering of the human inferior parietal lobule by whole-brain connectivity mapping of resting-state functional magnetic resonance imaging signals. Brain Connectivity 4, 53–69.
Zhang, X., Jiang, Y., Zhang, S., Li, F., Pei, C., He, G., Ao, M., Yao, D., Zhao, Y., Xu, P., 2020b. Correlation Analysis of EEG Brain Network with Modulated Acoustic Stimulation for Chronic Tinnitus Patients. IEEE Trans. Neural Syst. Rehabil. Eng. PP.
Zumsteg, D., Lozano, A.M., Wennberg, R.A, 2006. Mesial temporal inhibition in a patient with deep brain stimulation of the anterior thalamus for epilepsy. Epilepsia 47, 1958–1962.
Zumsteg, D., Wennberg, R.A., Treyer, V., Buck, A., Wieser, H.G, 2005. H2(15)O or 13NH3 PET and electromagnetic tomography (LORETA) during partial status epilepticus. Neurology 65, 1657–1660.