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Deafferentation-based pathophysiological differences in phantom sound: Tinnitus with and without hearing loss

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ABSTRACT

Tinnitus has been considered an auditory phantom percept. Recently a theoretical multiphase compensation mechanism at a cortical level has been hypothesized linking auditory deafferentation to tinnitus. This Bayesian brain model predicts that two very different kinds of tinnitus should exist, depending on the amount of hearing loss: an auditory cortex related form of tinnitus not associated with hearing loss, and a (para)hippocampal form associated with hearing loss, in which the auditory cortex might be of little relevance. In order to verify this model, resting state source analyzed EEG recordings were made in 129 tinnitus patients, and correlated to the mean hearing loss, the range of the hearing loss and the hearing loss at the tinnitus frequency. Results demonstrate that tinnitus can be linked to 2 very different mechanisms. In patients with little or no hearing loss, the tinnitus seems to be more related to auditory cortex activity, but not to (para)hippocampal memory related activity, whereas in tinnitus patients with more severe hearing loss, tinnitus seems to be related to (para)hippocampal mechanisms. Furthermore hearing loss seems to drive the communication between the auditory cortex and the parahippocampus, as measured by functional and effective connectivity.

Introduction

Non-pulsatile tinnitus is the perception of a sound in the absence of a corresponding external sound source, and is therefore considered as an auditory phantom percept (Eggermont and Roberts, 2004; Jastreboff, 1990). Typically this has been related to an auditory deafferentation such as in noise trauma, presbyacusis, or other causes of auditory deprivation. Recently, a theoretical multiphase compensation mechanism at a cortical level has been hypothesized linking auditory deafferentation to tinnitus (De Ridder et al., 2014a). The theoretical model is based on the concept of the Bayesian brain, which expresses the view that our brain's main function is to reduce uncertainty which is inherently present in a changing environment (Friston, 2010). It does so by updating of memory-based prior beliefs about the world through acquiring new information from the environment via the senses (Knill and Pouget, 2004). Humans and other animals operate in a changing environment, thus in a world of sensory uncertainty. Uncertainty is a state in which a given representation of the world cannot be used as a guide to subsequent behavior, cognition or emotional processing (Harris et al., 2008). However, the environment is not completely random and recurring patterns can be predicted based on stored experience and the brain must process the uncertainty to generate perceptual representations of the world and guide future actions (Knill and Pouget, 2004). Thus, the brain must represent and use information about uncertainty in its computations for perception and action. Von Helmholtz suggested that the real world was a hypothesis or prediction. Bayes adds to that that perception is to be seen as an updated prediction by actively sampling the environment, as Bayesian inference. The Bayesian coding hypothesis states that the brain represents sensory information probabilistically, in the form of probability distributions and that perception is a process of probabilistic inference (Knill and Pouget, 2004). In order to reduce uncertainty, the brain has a model of the world that it tries to optimize using sensory inputs (Friston, 2010). In this view, the brain is an inference machine that actively predicts and explains its sensations. In other words, the brain makes predictions about what it is likely to encounter next, so it can respond efficiently to changes in the environment. It updates the prediction in a Bayesian way by actively sampling the environment. Bayesian inference can thus be conceptualized as the use of sensory information from the environment to update memory-based prior beliefs about the state of the world (i.e. beliefs that are held before sensory inputs are acquired) to produce posterior beliefs (i.e. beliefs that emerge after inputs have been acquired). These posterior beliefs are what we perceive, and they become the new prediction against which the next sensory inputs will be compared.

Auditory deafferentation limits the amount of information the brain can acquire to make sense of the world. In other words, auditory

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deafferentation increases the (auditory) uncertainty of the environment. In order to minimize uncertainty, the deafferented brain area will attempt to obtain the missing information or fill in the missing information (De Ridder et al., 2014a). The model hypothesizes that deprived auditory information depends on the amount (bandwidth) of deafferented auditory channels. In a very limited amount of receptor loss, a selective increase of cortical excitability, either via increased excitatory tone or via reduced inhibitory tone will suffice (Rajan, 1998), and the missing information can be obtained via access of overlapping tuning curves of the neighboring cortical cells. If the deafferentation is somewhat larger a widening of auditory receptive fields (Chen et al., 1996) will permit to pull the missing information from the auditory cortical neighborhood. If this is insufficient, due to a still larger deafferentation, dendritic and axonal rewiring can occur (Hsieh et al., 2007), and if that doesn't work the missing auditory information can be pulled from (para)hippocampal memory (De Ridder et al., 2014a). This model explains why not all forms of tinnitus are related to topographical map reorganization (Langers et al., 2012), and predicts that in hearing loss which is too large for filling in via auditory cortex mediated plasticity, the (para)hippocampus becomes involved. The parahippocampal area can be considered as the main node of entry for auditory information to the medial temporal lobe memory system, where salient information is encoded into long-term memory (Engelien et al., 2000). The parahippocampal area has been hypothesized to play a central role in memory recollection, sending information from the hippocampus to the association areas, which might explain it involvement in the generation of simple auditory phantom percepts such as tinnitus (De Ridder et al., 2011a). The parahippocampal area has been implicated in tinnitus, both in EEG (De Ridder et al., 2011c; Joos et al., 2012; Moazami-Goudarzi et al., 2010; Vanneste and De Ridder, 2011a, 2012; Vanneste et al., 2010a, c, 2011a), PET (Schecklmann et al., 2011; Song et al., 2012) and resting state fMRI (rsfMRI) (Maudoux et al., 2012a, 2012b; Schmidt et al., 2013) studies, and parahippocampal-auditory cortex functional connectivity is consistently present in functional imaging studies related to tinnitus, both in MEG (Schlee et al., 2009), EEG (Vanneste et al., 2011b) and rsfMRI (Maudoux et al., 2012a, 2012b; Schmidt et al., 2013).

The Bayesian brain model thus predicts that different tinnitus generating mechanisms should exist based on the amount of hearing loss. It can be hypothesized that the parahippocampal area becomes involved in tinnitus associated with audiometrically detectable hearing loss. That is, limited damage to auditory receptors (i.e. increase of auditory uncertainty) can be compensated, i.e. filled-in, within the auditory cortex by local hyperactivity and local map plasticity. However, in patients with severe hearing loss, when local auditory cortical map plasticity cannot recruit the missing information from the auditory cortical neighborhood, auditory memory related areas become more involved to fill in the missing information. Hence, the model predicts that in tinnitus associated with more severe hearing loss the parahippocampus becomes more involved as a tinnitus generating mechanism, whereas in tinnitus without hearing loss the auditory cortex should be more involved. The aim of this study is to verify whether there is scientific support for the theoretical Bayesian tinnitus model proposed (De Ridder et al., 2014a).

Methods and materials

Subjects

Selection was based on the availability of both audiometric and EEG data of a consecutive group of recently evaluated tinnitus patients, in order to prevent a selection bias. Individuals with pulsatile tinnitus, Ménière's disease, otosclerosis, chronic headache, neurological disorders such as brain tumors, traumatic brain injury or stroke and individuals being treated for mental disorders were not included in the study in order to increase the sample homogeneity. Data of 129 tinnitus patients ($M = 49.67$ years; $Sd = 14.68$; 91 males and 38 females) were included from a database of the TRI multidisciplinary tinnitus clinic in Antwerp, Belgium. See Table 1 for an overview of the tinnitus characteristics.

All patients were interviewed as to the perceived location of the tinnitus (the left ear, in both ears, the right ear) as well as the tinnitus sound characteristics (pure tone-like tinnitus or noise-like tinnitus). In addition, all patients were screened for the extent of hearing loss (dB HL) using a pure tone audiometry using the British Society of Audiology procedures at .125 kHz, .25 kHz, .5 kHz, 1 kHz, 2 kHz, 3 kHz, 4 kHz, 6 kHz and 8 kHz (Audiology, 2008). Based on this audiogram we calculated both the mean hearing loss by taking the average of the hearing loss over all frequencies measured. The tinnitus patients were subsequently separated on the amount of hearing loss. That is, we set the threshold for dividing patients into the little or no hearing loss group at ≤ 20 dB HL ($n = 48$) and more severe hearing loss at > 20 dB HL ($n = 81$) (Farrior, 1956). In addition, we also calculated the range/width of the hearing loss by counting the amount of audiometric frequencies with a hearing loss > 20 dB HL based on a routine clinical audiometry.

Tinnitus patients were further tested for the tinnitus pitch (frequency) by performing a tinnitus matching analysis. In unilateral tinnitus patients, tinnitus matching was performed contralateral to the tinnitus ear. In bilateral tinnitus patients, tinnitus matching was performed contralateral to the worst tinnitus ear. First, a 1 kHz pure tone was presented contralateral to the (worst) tinnitus ear at 10 dB above the patient's hearing threshold in that ear. The pitch was adjusted until the patient judged the sound to resemble his/her tinnitus most (Meeus et al., 2009, 2011). Based on the tinnitus frequency, we calculated the hearing loss at the tinnitus frequency as obtained by tinnitus matching. For unilateral tinnitus the hearing loss contralateral to where the patient perceived the tinnitus was considered, while for bilateral tinnitus patients we calculated the mean of hearing thresholds. A numeric rating scale for loudness ('How loud is your tinnitus?': 0 = no tinnitus and 10 = as loud as imaginable') was assessed as well as the Dutch translation of the Tinnitus Questionnaire (TQ) (Meeus et al., 2007). This scale is comprised of 52 items and is a well-established measure for the assessment of a broad spectrum of tinnitus-related psychological complaints. The TQ measures emotional and cognitive distress, intrusiveness, auditory perceptual difficulties, sleep disturbances, and somatic complaints. As previously mentioned, the global TQ score can be computed to measure the general level of psychological and psychosomatic distress. In several studies, this measure has been shown to be a reliable and valid instrument in different countries (Hiller and Goebel, 1992; McCombe et al., 2001). A 3-point scale is given for all items, ranging from 'true' (2 points) to 'partly true' (1 point) and 'not true' (0 points). The total score (from 0 to 84) was computed according to standard criteria published in previous work

Table 1
Tinnitus characteristics

Lateralization	
Left	19
Right	18
Bilateral	92
Tone	
Pure tone	59
Noise Like	70
Tinnitus loudness	
Mean	5.22
Sd	2.40
Tinnitus distress	
Mean	35.97
Sd	16.83
Mean Hearing loss	
Mean	27.91
Sd	17.08
Range of the hearing loss	
Mean	9.41
Sd	5.1
Hearing loss at the tinnitus frequency	
Mean	40.84
Sd	26.75

(Hiller and Goebel, 1992; Hiller et al., 1994; Meeus et al., 2007). Based on the total score on the TQ, patients can be assigned to a distress category: slight (0–30 points; grade 1), moderate (31–46; grade 2), severe (47–59; grade 3), and very severe (60–84; grade 4) distress. Goebel and Hiller stated that grade 4 tinnitus patients are psychologically decompensated, indicating that patients categorized into this group cannot cope with their tinnitus (Goebel and Hiller, 1994). In contrast, patients that have a score lower than 60 on the TQ can cope with their tinnitus. See Table 1 for an overview of the tinnitus characteristics.

Healthy control group

Group age and gender matched EEG data of a healthy control group (N = 129; *M* = 48.75 years; *Sd* = 13.20; 91 males and 38 females) was collected. None of these subjects was known to suffer from tinnitus. Exclusion criteria were known psychiatric or neurological illness, psychiatric history or drug/alcohol abuse, history of head injury (with loss of consciousness) or seizures, headache, or physical disability. For these healthy controls hearing assessment was not available.

Pearson correlation

Pearson correlations were calculated between the tinnitus loudness and the mean hearing loss, the range of the hearing loss and the hearing loss at the tinnitus frequency. In addition Pearson correlations were calculated between tinnitus loudness, the mean hearing loss, the range of the hearing loss and the EEG activity and functional connectivity in the auditory cortex and parahippocampus respectively.

EEG Data collection

EEG data were obtained as a standard procedure. Recordings were obtained in a fully lighted room with each participant sitting upright on a small but comfortable chair. The actual recording lasted approximately five min. The EEG was sampled using Mitsar-201 amplifiers (NovaTech http://www.novatecheeg.com/) with 19 electrodes placed according to the standard 10–20 International placement (Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, O2), analogous to what is was done in the normative group. Impedances were checked to remain below 5 kΩ. Data were collected eyes-closed (sampling rate = 500 Hz, band passed 0.15–200 Hz). Off-line data were resampled to 128 Hz, band-pass filtered in the range 2–44 Hz and subsequently transposed into Eureka! software (Congedo, 2002), plotted and carefully inspected for manual artifact-rejection. All episodic artifacts including eye blinks, eye movements, teeth clenching, body movement, or ECG artifact were removed from the stream of the EEG. Average Fourier cross-spectral matrices were computed for 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). These frequency bands are based on previous research in tinnitus (Vanneste and De Ridder, 2011b; Vanneste et al., 2010c, 2011a,b).

Source localization

Standardized low-resolution brain electromagnetic tomography (sLORETA; Pascual-Marqui, 2002) was used to estimate the intracerebral electrical sources. As a standard procedure a common average reference transformation (Pascual-Marqui, 2002) is performed before applying the sLORETA algorithm. sLORETA computes electric neuronal activity as current density (A/m^2) without assuming a predefined number of active sources. The solution space used in this study and associated leadfield matrix are those implemented in the LORETA-Key software (freely available at http://www.uzh.ch/keyinst/loreta.htm). This software implements revisited realistic electrode coordinates (Jurcak et al., 2007) and the lead field produced by Fuchs et al. (2002) applying the boundary element method on the MNI-152 (Montreal neurological institute, Canada). The sLORETA-key anatomical template divides and labels the neocortical (including hippocampus and anterior cingulated cortex) MNI-152 volume in 6239 voxels of dimension 5 mm^3, based on probabilities returned by the Demon Atlas (Lancaster et al., 2000). The co-registration makes use of the correct translation from the MNI-152 space into the Talairach and Tournoux space.

Lagged Phase Coherence

Coherence and phase synchronization between time series corresponding to different spatial locations are usually interpreted as indicators of the "connectivity". However, any measure of dependence is highly contaminated with an instantaneous, non-physiological contribution due to volume conduction (Pascual-Marqui, 2007b). However, Pascual-Marqui (2007a) introduced new measures of coherence and phase synchronization taking into accounts only non-instantaneous (lagged) connectivity, effectively removing the confounding factor of volume conduction. Such "lagged phase coherence" between two sources can be interpreted as the amount of cross-talk between the regions contributing to the source activity (Congedo et al., 2010). Since the two components oscillate coherently with a phase lag, the cross-talk can be interpreted as information sharing by axonal transmission. More precisely, the discrete Fourier transform decomposes the signal in a finite series of cosine and sine waves at the Fourier frequencies (Bloomfield, 2000). The lag of the cosine waves with respect to their sine counterparts is inversely proportional to their frequency and amounts to a quarter of the period; for example, the period of a sinusoidal wave at 10 Hz is 100 ms. The sine is shifted a quarter of a cycle (25 ms) with the respect to the cosine. Then the lagged phase coherence at 10 Hz indicates coherent oscillations with a 25 ms delay, while at 20 Hz the delay is 12.5 ms, etc. The threshold of significance for a given lagged phase coherence value according to asymptotic results can be found as described by Pascual-Marqui (2007a, 2007b), where the definition of lagged phase coherence can be found as well. As such, this measure of dependence can be applied to any number of brain areas jointly, i.e., distributed cortical networks, whose activity can be estimated with sLORETA. Measures of linear dependence (coherence) between the multivariate time series are defined. The measures are non-negative, and take the value zero only when there is independence and are defined in the frequency domain: 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). Based on this principle lagged linear connectivity was calculated. Time-series of current density were extracted for different region of interests using sLORETA. Power in all 6239 voxels was normalized to a power of 1 and log transformed at each time point. Region of interest values thus reflect the log transformed fraction of total power across all voxels, separately for specific frequencies. Regions of interest selected were the left auditory cortex (BA41, BA42), right auditory cortex (BA41, BA42) and the left parahippocampus (BA27) and right parahippocampus (BA27). The selection of these regions of interest was based on the Bayesian brain model as introduced in the introduction (a priori) and confirmed by the comparison of activity between the tinnitus groups with little or no hearing loss and tinnitus with a more severe hearing loss (a posteriori)

Statistical analyses on the whole brain

The methodology used is a non-parametric permutation test. It is based on estimating, via randomization, the empirical probability distribution for the max-statistic, under the null hypothesis comparisons (Nichols and Holmes, 2002). This methodology corrects for multiple testing (i.e. for the collection of tests performed for all voxels, and for all frequency bands). Due to the non-parametric nature of this method, its validity does not rely on any assumption of Gaussianity (Nichols and

Holmes, 2002). The significance threshold for all tests was based on a permutation test with 5000 permutations. Comparisons were made between the healthy controls versus tinnitus group with little or no hearing loss, healthy controls versus tinnitus with more severe hearing loss, and between the tinnitus groups with little or no hearing loss and tinnitus with a more severe hearing loss. These comparisons were performed on a whole brain by sLORETA statistical contrast maps through multiple voxel-by-voxel comparisons in a logarithm of *t*-ratio. Correlations are calculated between the mean hearing loss, the range of the hearing loss and the hearing loss at the tinnitus frequency respectively with brain activity (whole brain analysis) for the different frequency bands. Again the significance threshold was based on a permutation test with 5000 permutations.

Statistical analyses for the lagged phase coherence

Lagged phase synchronization/coherence or functional connectivity contrast maps were calculated and correlated with the mean hearing loss, the range of the hearing loss and the hearing loss at the tinnitus frequency for the different frequency bands. The significance threshold was based on a permutation test with 5000 permutations. This methodology corrects for multiple testing (i.e. for the collection of tests performed for all voxels, and for all frequency bands).

Granger causality

Granger causality reflects the strength of effective connectivity (i.e. causal interactions, extract activity of one are of causal influences of one neural element over another) from one region to another by quantifying how much the signal in the seed region is able to predict the signal in the target region (Geweke, 1982; Granger, 1969). In other words it can be considered as a directional functional connectivity. Granger causality is defined as the log-ratio between the error variance of a reduced model, which predicts one time series based only on its own past values, and that of the full model, which in addition includes the past values of another time series. It is important to note that Granger causality does not imply anatomical connectivity between regions but directional functional connectivity between two sources. A comparison was made between healthy controls, tinnitus patients with no or mild hearing loss and tinnitus patients with more severe hearing loss on Granger causality outcome measure using a one-way ANOVA. In addition, we calculated the Granger causality between a control area (left primary visual cortex) and the left and right parahippocampus.

Pearson correlations were calculated between the Granger causality outcome measures per patient and respectively the mean hearing loss, the range of the hearing loss and the hearing loss at the tinnitus frequency based on lagged phase coherence outcome. In addition, partial correlations were obtained between Granger causality outcome measures per patient and respectively the mean hearing loss, the range of the hearing loss and the hearing loss at the tinnitus frequency, based on lagged phase coherence outcome controlling of loudness and age. We corrected for the amount of regions of interest using a Bonferroni correction.

Correlations

Pearson correlations were calculated between the region of interest and the loudness for 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). This analysis was corrected for the amount of pairwise comparisons using a Bonferroni correction.

Results

Behavioral measures

A Pearson correlation between the mean hearing loss and the range of the hearing loss revealed a significant and very strong positive correlation ($r = .87$, $p < .001$) indicating that the larger the mean hearing loss is the wider it is. A correlation between the tinnitus loudness and the mean hearing loss for the entire group also revealed a significant but weaker positive correlation ($r = .35$, $p < .001$). In addition a correlation was computed between the tinnitus loudness and the range of the hearing loss. This analyses also revealed a significant effect ($r = .31$, $p < .001$). Correlation analysis between the tinnitus loudness and the hearing loss at the tinnitus frequency did not reveal a significant effect ($r = .12$, $p = .10$). A correlation between the hearing loss at the tinnitus frequency and respectively the mean hearing loss ($r = .37$, $p < .001$) and the range of the hearing loss ($r = .35$, $p < 001$) revealed both significant positive correlations. See Fig. 1 for an overview.

Tinnitus patients with little or no hearing loss ($M = 32.67$, $Sd = 17.32$) and tinnitus patients with severe hearing loss ($M = 37.93$, $Sd = 16.32$) revealed no significant difference for distress ($F = 2.98$, $p = .09$). A difference was obtained for the age ($F = 8.30$, $p = .005$) and age of onset ($F = 68.26$, $p < .001$). Tinnitus patients with little or no hearing loss (Age: $M = 38.44$, $Sd = 12.59$; and age of onset: $M = 6.96$, $Sd = 7.93$) are younger and have tinnitus for a shorter time in comparison to tinnitus patients with severe hearing loss (Age: $M = 56.33$, $Sd = 11.46$; and age of onset: $M = 56.93$, $Sd = 11.46$). No significant difference was obtained between tinnitus patients with little or no hearing loss and tinnitus patients with severe hearing loss for tinnitus lateralization ($\chi^2 = .51$, $p = .48$) or tinnitus type ($\chi^2 = .01$, $p = .99$).

Whole brain analysis

Little or no hearing loss versus healthy controls

A comparison between tinnitus patients with a little or no hearing loss versus healthy controls revealed a significant effect for the theta frequency ($t = 2.58$, $p < .05$) at the left anterior midtemporal (i.e. tertiary auditory) cortex (see Fig. 2A). No significant effects were obtained for the delta, theta, alpha1, alpha2, beta1, beta2 and beta3 frequency bands.

Severe hearing loss versus healthy controls

A comparison between tinnitus patients with severe hearing loss revealed a significant effect for theta frequency ($t = 2.49$, $p < .05$) over the parahippocampal brain area (see Fig. 2B). No significant effects were obtained for the delta, alpha1, alpha2, beta1, beta2, beta3 and gamma frequency bands.

Little or no versus more severe hearing loss

A comparison between tinnitus patients with a little or no versus more severe hearing loss revealed that tinnitus patients with a more severe hearing loss a decreased activity over the left anterior midtemporal (i.e. tertiary auditory) cortical areas at the gamma frequency band in comparison to tinnitus patients with a little or no hearing loss ($t = 3.07$, $p < .01$) (Fig. 3). No significant effect was obtained for the other 7 frequency bands.

Additional analysis

For the group with severe hearing loss, we made a comparison between subjects who have an average hearing loss between 20 and 40 dB and subjects with an average hearing loss of more than 40 dB. This comparison revealed no significant effects for the delta, alpha1, alpha2, beta1, beta2, beta3 and gamma frequency bands.

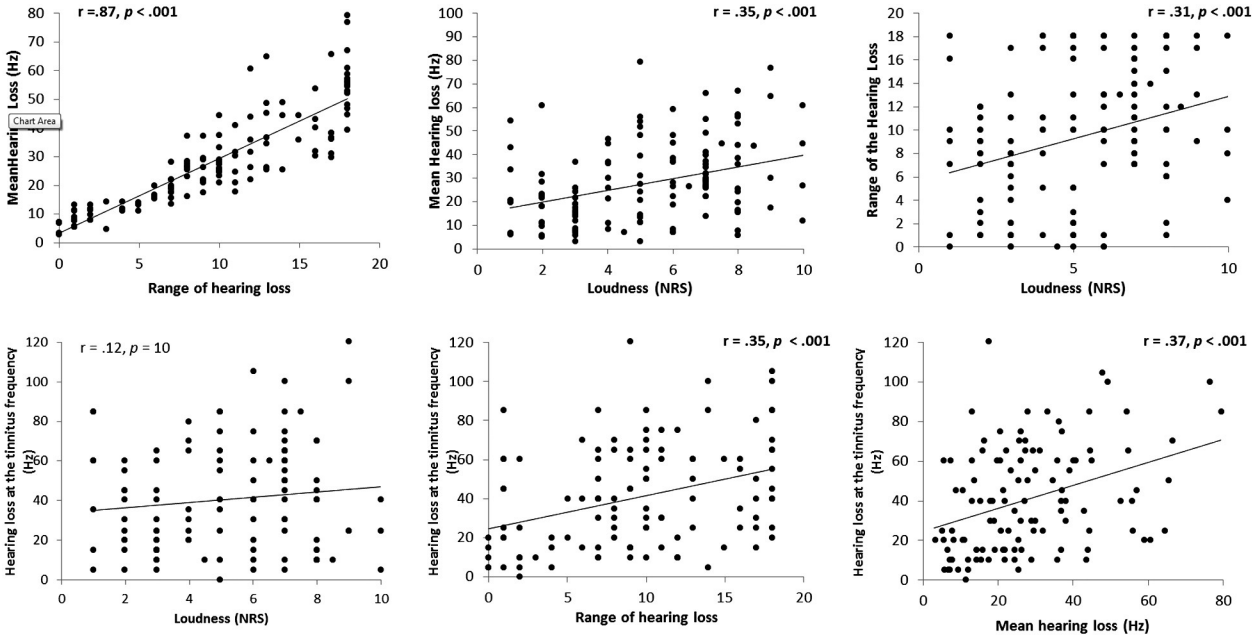


Fig. 1. Pearson correlations between the range of hearing loss (i.e. range/width of the hearing loss by counting the amount of audiometric frequencies with a hearing loss >20 dB HL) and respectively the mean hearing loss and the hearing loss at the tinnitus frequency and between the tinnitus loudness and respectively the mean hearing loss, the hearing loss at the tinnitus frequency and the range of the hearing loss.

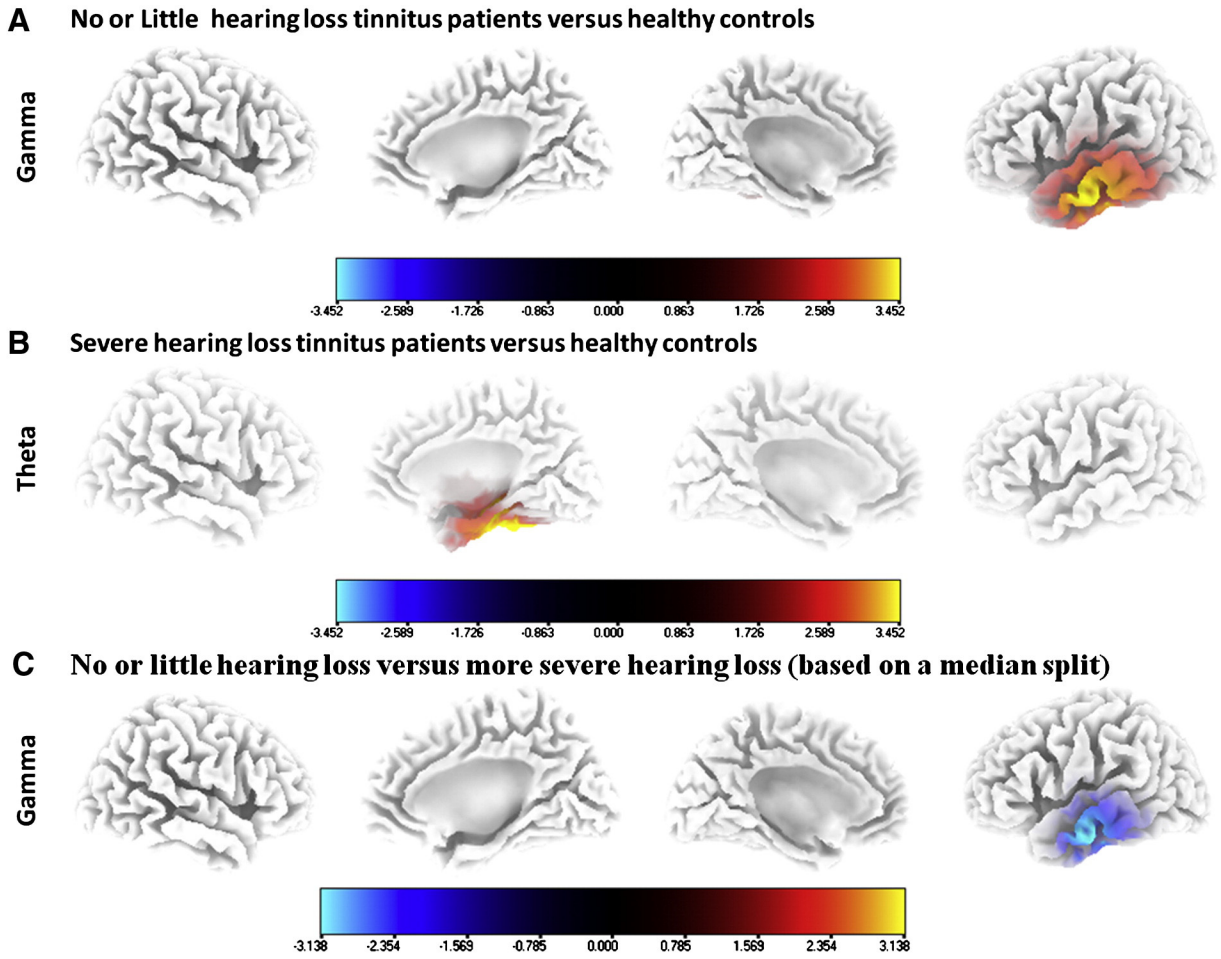


Fig. 2. (A) A comparison between little or no hearing loss tinnitus patients and healthy controls revealed a significant difference in gamma activity at the left anterior midtemporal (tertiary auditory) cortex for the gamma frequency band. (B) A comparison between tinnitus patients with severe hearing loss and healthy controls revealed a significant difference in theta activity at the left parahippcampus. (C) A comparison between tinnitus patients with no or little hearing loss versus more severe hearing loss (based on a median split) revealed that tinnitus patients with a more severe hearing loss had a decreased activity in the left anterior midtemporal (tertiary auditory) cortex at the gamma frequency band in comparison to tinnitus patients with little or no hearing loss. (A threshold of <.05 was used).

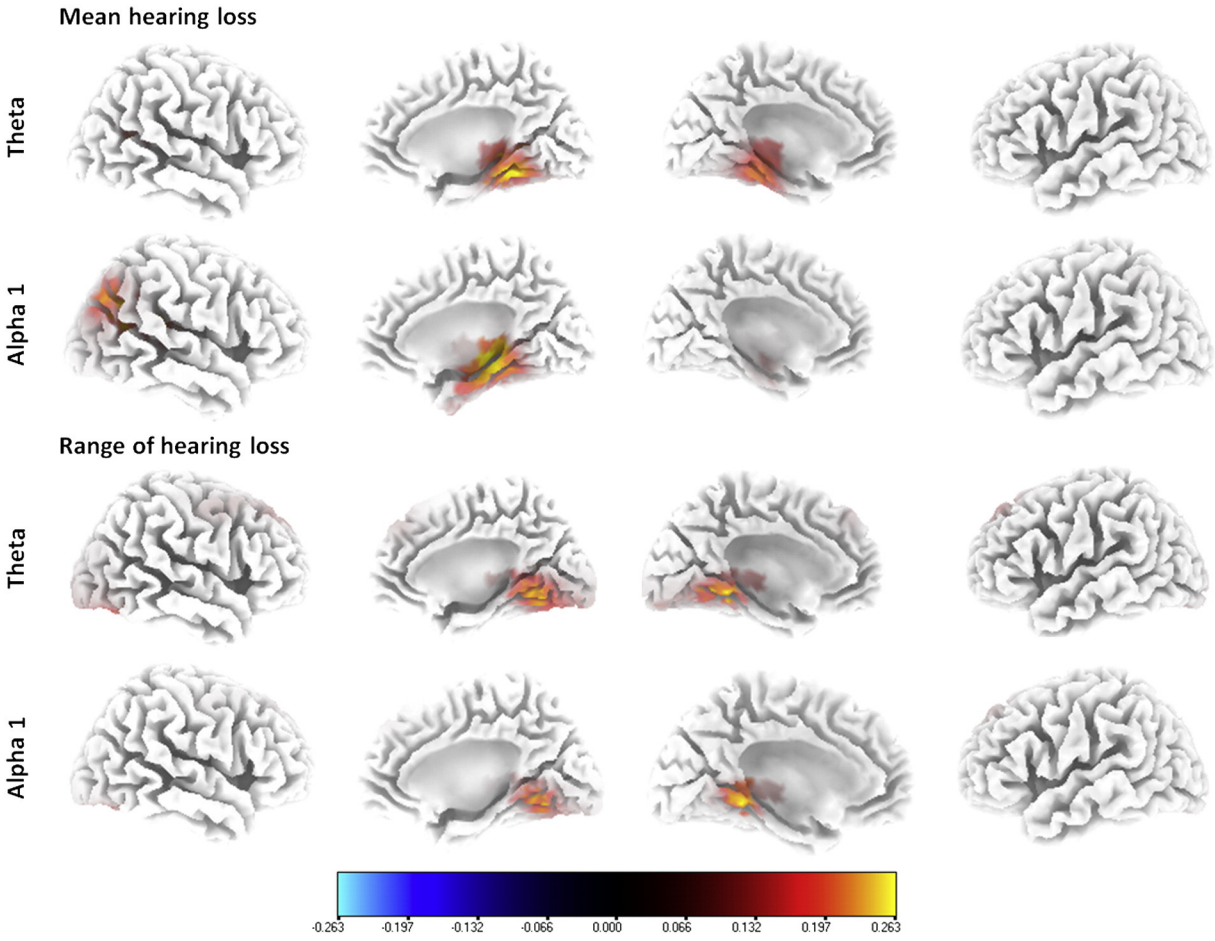


Fig. 3. Whole brain correlation analysis revealed a positive significant correlation between theta activity in the left and right parahippocampal area and mean hearing loss as well as the range of the hearing loss. A positive significant correlation between alpha1 activity in the left and right parahippocampal area and the range of hearing loss was noted as well, as was a positive significant correlation between alpha1 activity in the left parahippocampal area and the mean hearing loss. (A threshold of <.05 was used).

Whole brain correlation analysis in tinnitus patients

Mean hearing loss

A correlation analysis revealed a significant positive effect between the mean hearing loss and the left and right parahippocampal area at the theta frequency band ($r = .27$, $p < .01$) and the right parahippocampal area at the alpha 1 frequency band ($r = .21$, $p < .01$)(Fig. 3). No significant effect was obtained for the other delta, alpha2, beta1, beta2, beta3 and gamma frequency band frequency bands.

Range of hearing loss

A correlation analysis with the range of hearing loss revealed a significant positive effect between the range of hearing loss and the left and right parahippocampal area at the theta frequency band ($r = .26$, $p < .01$) and the left and right parahippocampal area at the alpha 1 frequency band ($r = .28$, $p < .01$)(Fig. 3). No significant effect was obtained for the other delta, alpha2, beta1, beta2, beta3 and gamma frequency band frequency bands.

Hearing loss at the tinnitus frequency

A whole brain correlation analysis revealed no significant effects for the hearing loss at the tinnitus frequency for the delta, theta, alpha1, alpha2, beta1, beta2, beta3 and gamma frequency bands.

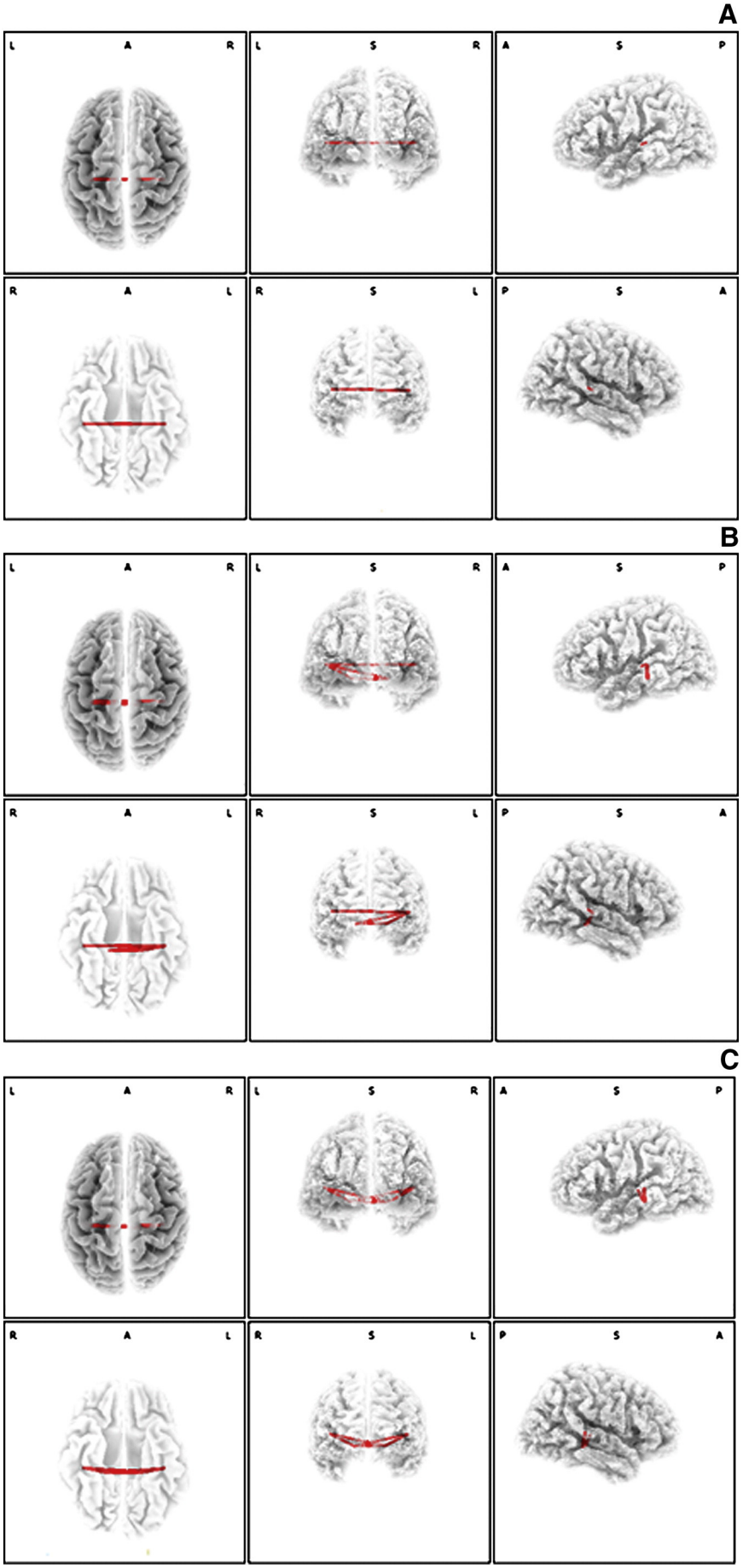
Lagged phase coherence

Little or no hearing loss versus healthy controls

A functional connectivity (FC) analysis by measuring lagged phase synchronization was conducted with the auditory cortex and parahippocampus as ROIs. The FC was compared between tinnitus patients with little or no hearing loss and healthy controls. This analysis revealed that tinnitus patients with little or no hearing loss have stronger FC between the left auditory cortex and right auditory cortex for the gamma frequency band ($t = 3.04$, $p < .01$) (Fig. 4A). No significant effect was obtained for the delta, theta, alpha1, alpha2, beta1, beta2, and beta3 frequency band frequency bands.

Severe hearing loss versus healthy controls

A similar FC analysis was conducted looking at the lagged phase synchronization/coherence between the left and right parahippocampus and the left and right auditory cortex for tinnitus patients with severe hearing loss in comparison to healthy controls. This analysis demonstrated a significant effect for theta and alpha1 theta frequency band, indicating that tinnitus patients with severe hearing loss have increased FC between the right and left parahippocampi and the left and right auditory cortex for the theta and alpha1 frequency band ($t = 2.61$, $p < .05$) (Fig. 4B). No significant effect was obtained for the other delta, alpha2, beta1, beta2, beta3 and gamma frequency band frequency bands.


A
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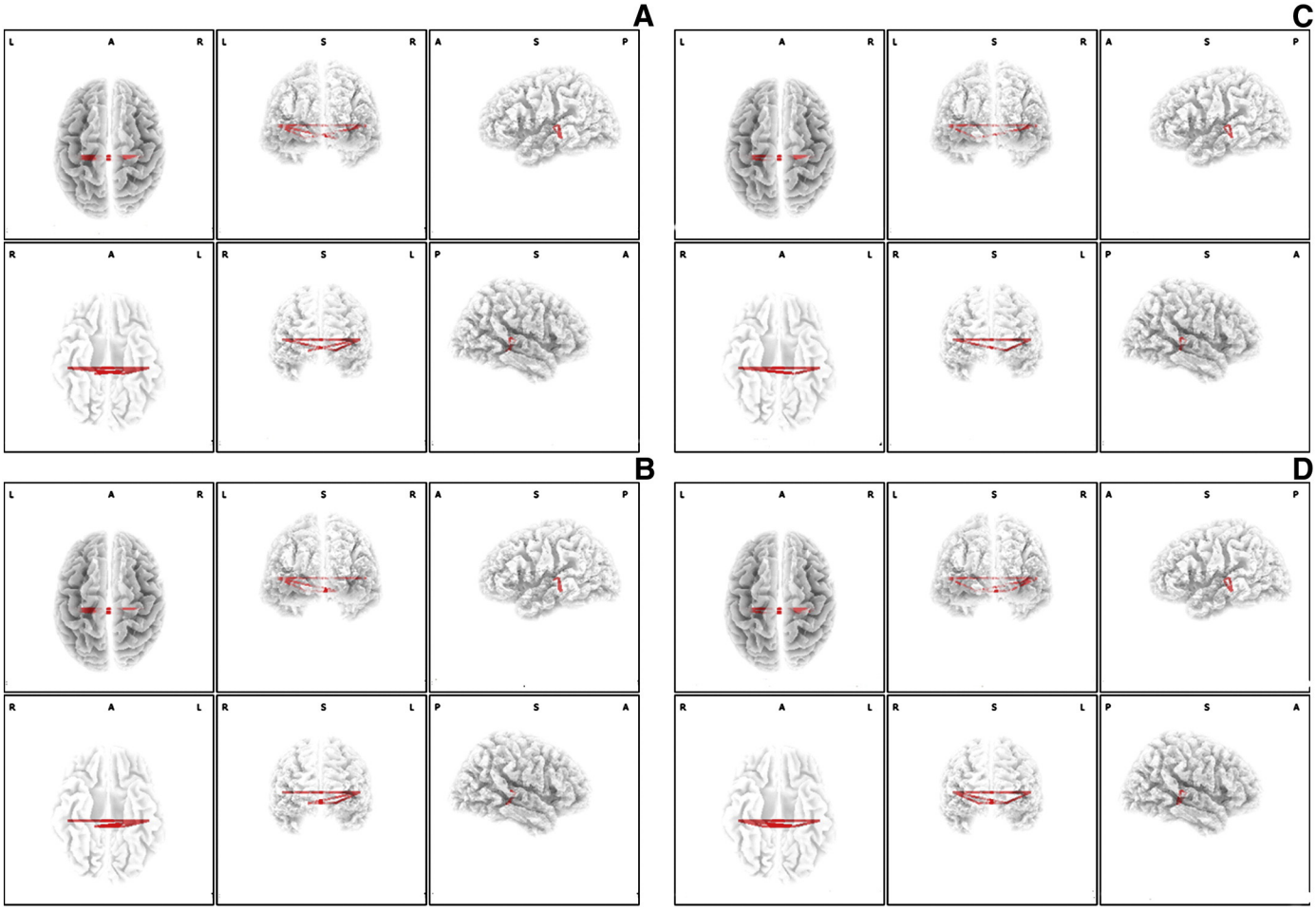

Fig. 5. Increased lagged phase synchronization (=functional connectivity) between the auditory cortex and the parahippocampus for (A) theta and (B) alpha1 frequency band correlates with the mean hearing loss. Increased functional connectivity between the auditory cortex and the parahippocampus for (C) theta and (D) alpha1 frequency band correlates with the range of the hearing loss. (A threshold of <.05 was used).

Little or no versus more severe hearing loss

Again FC analysis was conducted looking at the lagged phase synchronization/coherence between the left and right parahippocampus and the left and right auditory cortex for tinnitus patients with severe hearing loss in comparison to tinnitus patients with little or no hearing loss. This analysis demonstrated a significant effect for theta and alpha1 theta frequency band, indicating that tinnitus patients with severe hearing loss have increased FC between the right and left parahippocampi and the left and right auditory cortex for the theta and alpha1 frequency band ($t = 2.42$, $p < .05$) (Fig. 4C). No significant effect was obtained for the other delta, alpha2, beta1, beta2, beta3 and gamma frequency band frequency bands.

Additional Analysis

For the group with severe hearing loss, we made a comparison between subjects who have an average hearing loss between 20 and 40 dB and subjects with an average hearing loss of more than 40 dB. This comparison revealed no significant effects for the delta, alpha1, alpha2, beta1, beta2, beta3 and gamma frequency bands.

Lagged phase coherence correlations

Mean hearing loss

A correlation analysis was performed looking at the amount of amount of mean hearing loss and FC between the auditory cortex and parahippocampus. This analysis revealed that the higher the mean hearing loss was, the stronger the functional connectivity between the left parahippocampus and the left auditory cortex and right auditory cortex ($r = .22$, $p < .05$) as well as between the right parahippocampus and the left auditory cortex for the theta ($r = .16$, $p < .05$; Fig. 5A) and between the left and right parahippocampus and the left auditory cortex for alpha1 ($r = .19$, $p < .05$; Fig. 5B) frequency band. No significant effect was obtained for the other delta, alpha2, beta1, beta2, beta3 and gamma frequency band frequency bands.

Range of hearing loss

A similar correlation analysis was conducted to verify how the range of hearing loss mediates the functional connectivity as measured by the lagged phase coherence between the left and right parahippocampus and the left and right auditory cortex. This

Fig. 4. Increased lagged phase synchronization (=functional connectivity) in (A) gamma frequency band between the left and right auditory cortex for tinnitus patients with no or little hearing loss in comparison to healthy controls. Increased functional connectivity between the auditory cortex and the parahippocampus for the (B) theta and (C) alpha1 frequency band in tinnitus patients with severe hearing loss in comparison to healthy controls. (A threshold of <.05 was used).

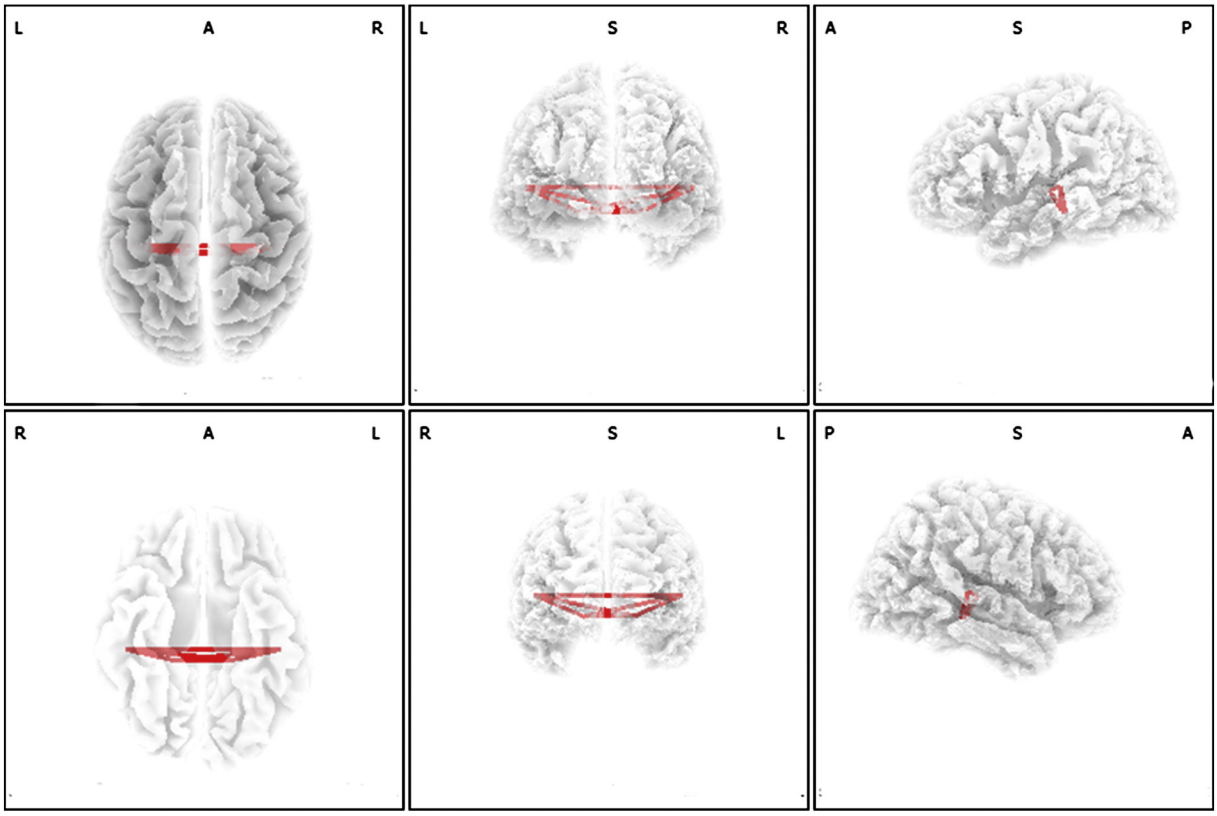

Fig. 6. Increased functional connectivity between the auditory cortex and the parahippocampus in the theta frequency band correlates with the hearing loss at the tinnitus frequency. (A threshold of <.05 was used).

correlation analysis demonstrated a significant effect for theta ($r = .17$, $p < .05$; Fig. 5C) and alpha1 theta ($r = .18$, $p < .05$; Fig. 5D) frequency band, indicating that the wider the range of the hearing loss was, the stronger the connectivity between the left parahippocampus and both auditory cortices for theta and for alpha1, as well as with added connectivity between the right and left parahippocampi and the right parahippocampus and right auditory cortex for alpha1. No significant effect was obtained for the other delta, alpha2, beta1, beta2, beta3 and gamma frequency band frequency bands.

Hearing loss at the tinnitus frequency

Again a correlation analysis was conducted demonstrating that the higher the hearing loss at the tinnitus frequency was, the stronger the functional connectivity between the left parahippocampus and the left and right auditory cortex as well as between the right parahippocampus

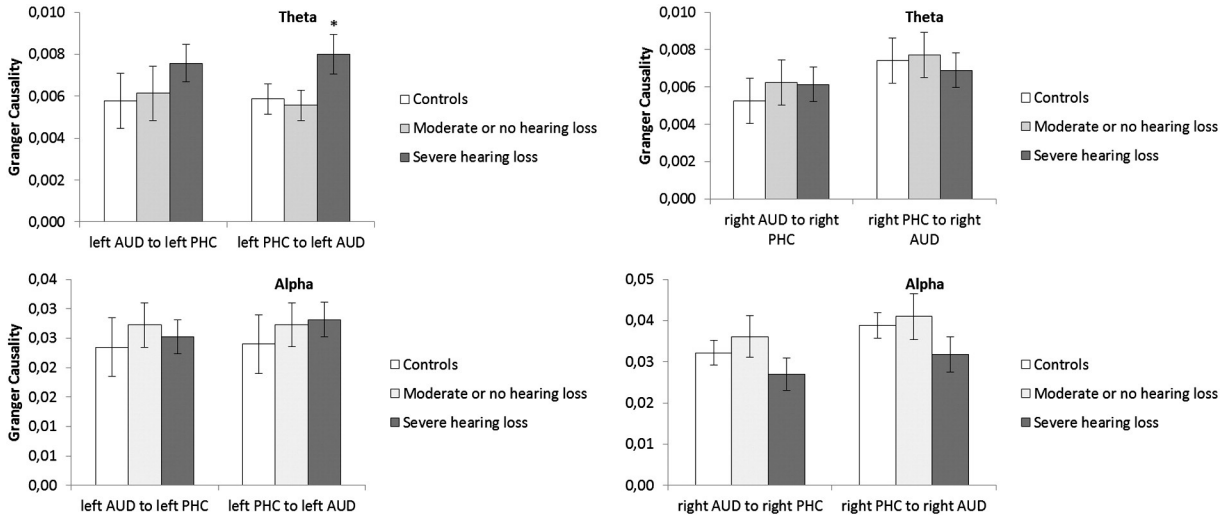

Fig. 7. A comparison between healthy controls, tinnitus patients with no or mild hearing loss and tinnitus patient with more severe hearing loss was made indicating a significant difference between groups for the theta frequency band for connection going from the left parahippocampus to the left auditory cortex ($F = 4.21$, $p = .02$) Granger causality was higher for tinnitus patient with more severe hearing loss in comparison to healthy controls ($t = 3.09$, $p = .01$) and tinnitus patients with no or mild hearing loss ($t = 2.91$, $p = .03$). No significant difference was obtained between healthy controls and tinnitus patients with no or mild hearing loss. No other significant effects were obtained.

and the left and right auditory cortices for the theta (r = .20, $p < .01$) frequency band (Fig. 6). No significant effect was obtained for the delta, alpha1, alpha2, beta1, beta2, beta3 and gamma frequency band frequency bands.

Granger Causality

A comparison between healthy controls, tinnitus patients with no or mild hearing loss and tinnitus patients with more severe hearing loss was made indicating a significant difference between groups for the theta frequency band for a connection going from the left parahippocampus to the left auditory cortex ($F = 4.21$, $p = .02$). Granger causality was higher for tinnitus patients with more severe hearing loss in comparison to healthy controls ($t = 3.09$, $p = .01$) and tinnitus patients with no or mild hearing loss ($t = 2.91$, $p = .03$). No significant difference was obtained between healthy controls and tinnitus patients with no or mild hearing loss. No other significant effects were obtained (see Fig. 7). In addition, we calculated the Granger causality for the control area (left primary visual cortex) and respectively left and right parahippocampus for healthy controls, tinnitus patients with no or mild hearing loss and tinnitus patients with more severe hearing loss. No significant difference was obtained between the 3 groups for the ganger causality from the left parahippocampus and the left primary visual cortex ($F = 1.22$, $p = .30$), from the left primary visual cortex and left parahippocampus ($F = .74$, $p = .39$), from the right parahippocampus and the left primary visual cortex ($F = 1.59$, $p = .21$), and from the left primary visual cortex and right parahippocampus ($F = .66$, $p = .44$).

Granger causality correlations

Mean hearing loss

Based on the lagged phase coherence connectivity analysis we focused on the two significant frequency bands, namely theta and alpha1 to calculate the directional connectivity (i.e. Granger causality) between the left auditory cortex and left parahippocampus as well as between the right auditory cortex and the right parahippocampus. The Granger causality correlated with the mean hearing loss demonstrated a positive correlation for the theta frequency band, indicating the more hearing loss a patient had the stronger the directionality was from the left parahippocampus to the left auditory cortex (r = .24, $p = .003$)(see Fig. 8A; Figure 1S). After correction for multiple comparisons the effect still remained. After a correcting for age, duration and loudness, a significant correlation was obtained between the left auditory cortex and left parahippocampus (r = .17, $p = .02$). No other significant results could be obtained as can been seen in Fig. 8A (& Figure 1S).

Range of hearing loss

A similar effective connectivity analysis was conducted for the range of the hearing loss. revealing a positive correlation for the theta frequency band, indicating the wider the hearing loss the stronger directionality there was from the left parahippocampus to the left auditory cortex (r = .23, $p = .005$)(see Fig. 8B; & Figure 2S). After correction for multiple comparisons the effect still remained. After a correcting for age, duration or loudness, a significant correlation was obtained between the left auditory cortex and left parahippocampus (r = .21, $p = .01$). No other significant results could be obtained as can been seen in Fig. 8B (& Figure 2S).

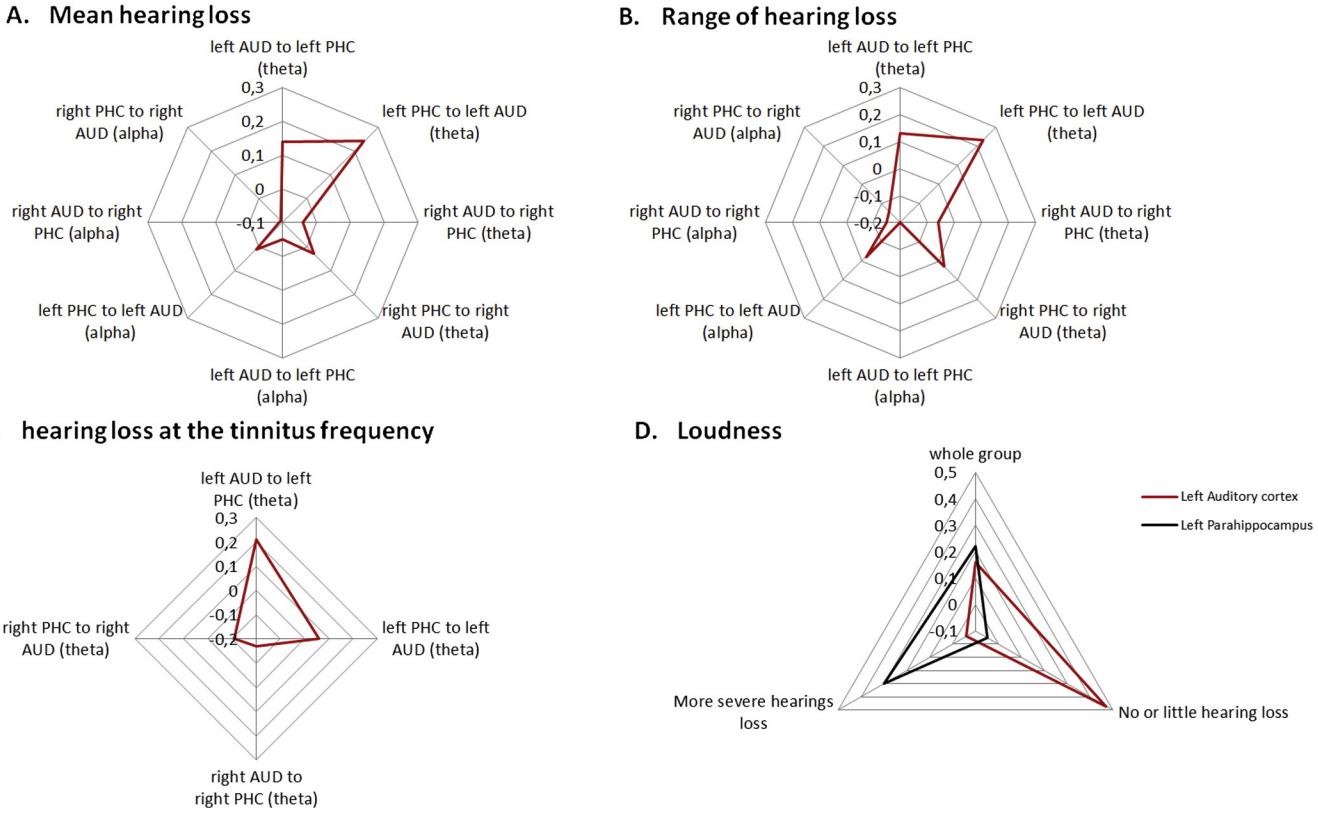

Fig. 8. (A-C) Correlation matrix for mean hearing loss, range of hearing loss and hearing loss at the tinnitus frequency directional connectivity (i.e. Granger causality) between the left auditory cortex and left parahippocampus as well as between the right auditory cortex and right parahippocampus. (D) Pearson correlation between respectively the left auditory cortex (AC) and the loudness for the gamma frequency as well as the left parahippocampus (PHC) and the loudness for the gamma frequency for the whole groups, the group with no or little hearing loss and more severe hearing loss. A significant correlation could be obtained for loudness and the left auditory cortex for whole groups as well as for no or little hearing loss as well as for loudness and the left parahippocampus for the whole group and severe hearing loss group. After correction for multiple comparisons (Bonferroni correction) the effect remained.

Hearing loss at the tinnitus frequency

Based on the lagged phase coherence connectivity analysis for the hearing loss at the tinnitus frequency we focused on the theta frequency bands and determined the Granger causality between the left auditory cortex and left parahippocampus as well as between the right auditory cortex and the right parahippocampus. This analysis showed a positive correlation for the theta frequency band from the left auditory cortex to the left parahippocampus ($r = .21$, $p = .013$). This suggests that the more hearing loss at tinnitus frequency the stronger the effective connectivity was from the left auditory cortex to the left parahippocampus (see Fig. 8C; Figure 3S). After correction for multiple comparisons the effect still remained. After a correcting for age, duration or loudness, a no significant correlation was obtained between the left auditory cortex and left parahippocampus. No significant other results could be obtained as can been seen in Fig. 8C (& Figure 3S). After correction for multiple comparisons the effect still remained.

Loudness

For the whole group a significant effect was obtained for the loudness with both the left auditory cortex ($r = .16$, $p = .03$) and the left parahippocampus ($r = .22$, $p = .006$) for the gamma frequency band (see Fig. 8D). When we look specifically at the group who had no or low hearing loss, we only found a significant correlation between the current density of the left auditory cortex and gamma frequency bands ($r = .47$, $p < .001$), but not for the parahippocampus (see Fig. 8D; Figure 4S). On the other hand a significant effect was obtained between the tinnitus loudness and the current density of the left parahippocampus for the gamma frequency bands in the group with severe hearing loss ($r = .30$, $p = .003$))(see Fig. 8D; Figure 4S). No significant correlation effect was obtained for the loudness with the current density of the left auditory cortex in the severe hearing loss group for the gamma frequency bands. The effect remained after correct for multiple comparisons.

After controlling for hearing loss, a significant effect was demonstrated between the loudness and current density of the left auditory cortex for the gamma frequency bands ($r = .47$, $p < .001$) for the group with no or a small amount of hearing loss. For the group with more severe hearing loss, a significant correlation could be obtained between the current density within the left parahippocampus and the loudness for the gamma frequency bands ($r = .29$, $p = .005$). No effect was obtained for the other frequency bands.

Age and age of onset

No significant effect was obtained for age and age of onset obtained for the delta, theta, alpha2, beta1, beta2, beta3 and gamma frequency band frequency bands for the left auditory cortex and left parahippocampus for the whole group. Looking at tinnitus patients with little or no hearing loss and tinnitus patients with severe hearing loss separately revealed no significant effect for age and age of onset for the delta, theta, alpha2, beta1, beta2, beta3 and gamma frequency band frequency bands for the left auditory cortex and left parahippocampus.

Discussion

The main finding of this study is that depending on the presence of hearing loss two different kinds of tinnitus can be discerned, an auditory cortex related tinnitus associated with little or no hearing loss and a parahippocampal one associated with hearing loss. Hearing loss and tinnitus have been linked, both pathophysiologically (Eggermont and Roberts, 2004; Jastreboff, 1990) and clinically (De Ridder et al., 2015a; Norena et al., 2002; Schecklmann et al., 2012b). The tinnitus pitch has indeed been linked to hearing loss (Norena et al., 2002), and especially steep sloping hearing loss is correlated with the presence of tinnitus (Demeester et al., 2007; Konig et al., 2006). In this study a correlation was obtained between the mean hearing loss, the range of the hearing loss and the hearing loss at the tinnitus frequency and the loudness of the tinnitus, respectively.

Both mean hearing loss and range of the hearing loss correlate with theta and alpha1 activity changes over the parahippocampal area on a whole brain analysis. This is interesting, as the parahippocampal area has been implicated as a gatekeeper to the hippocampus (Tulving and Markowitsch, 1997), functioning as a sensory gate for incoming irrelevant or redundant auditory input (Boutros et al., 2008). In view of the predictive Bayesian brain model this suggests that the more hearing loss is present, the more the parahippocampal sensory gate is opened, putatively pulling the phantom sound from hippocampal memory. This fits with human functional imaging studies that the (para)hippocampus is involved in both auditory memory (De Ridder et al., 2006; Grasby et al., 1993; Huijbers et al., 2011) and tinnitus (De Ridder et al., 2006; Landgrebe et al., 2009; Mirz et al., 2000; Vanneste and De Ridder, 2012). The auditory cortices are anatomically reciprocally connected to the parahippocampal area (Munoz-Lopez et al., 2010). In the parahippocampal area 35% of cells respond to complex auditory stimuli, and 2% specifically and selectively to auditory stimuli (Desimone and Gross, 1979; Kikuchi et al., 1997). Furthermore, when transiently suppressing (amygdalo)hippocampal activity in tinnitus patients by amytal injection in the anterior choroidal artery, tinnitus can be transiently suppressed (De Ridder et al., 2006). The question arises then whether this holds both for patients presenting with little or no and patients with severe hearing loss? A comparison between the 2 groups of tinnitus patients revealed that patients with more hearing loss had a decreased activity in the left anterior auditory cortex for the gamma frequency band in comparison to tinnitus patients with a little or no hearing loss. This was further confirmed by comparing tinnitus patients with no or little hearing loss and patient with severe hearing loss with healthy controls. While tinnitus patient with no or little hearing loss showed increased activity over the auditory cortex, tinnitus patient with severe hearing loss had increased activity over the parahippocampus. This suggests that in tinnitus patients with an important hearing loss, the auditory areas might be involved in a different way than in patients with little or no hearing loss. This is in line with the theoretical model where the missing auditory information can be retrieved from the auditory cortex as long as the deafferentation is not too large (De Ridder et al., 2014a). But the model also predicts that in patients with severe hearing loss, auditory memory related areas might become involved, in contrast to patients with little hearing loss. The reasoning is that if the missing auditory information cannot be retrieved via external input the predicted missing input will be pulled from memory. In addition, our data further indicate that in severe hearing loss the subjectively perceived tinnitus loudness is generated by the parahippocampus. While for tinnitus patients with a mild hearing loss, tinnitus loudness is more related to auditory cortex activity. These latter findings further suggest that the compensation mechanism to filling the missing information

Previous research already indicated that resting state functional connectivity between the auditory cortex and parahippocampal area, both on EEG (Vanneste and De Ridder, 2011a) and resting state fMRI (Maudoux et al., 2012b; Schmidt et al., 2013) is critically important in tinnitus. The subjectively perceived tinnitus loudness is related to the functional connectivity in theta between the left auditory cortex and posterior parahippocampal area, and more specifically to the percentage of time gamma band activity is nested (i.e. cross frequency coupled) on theta (De Ridder et al., 2015b). Anatomical studies of rhesus monkey revealed the existence of reciprocal connections between the auditory cortices and parahippocampal cortices (Engelien et al., 2000). Schmidt et al. (2013) recently showed that the left parahippocampus was more strongly connected with the auditory cortex in tinnitus patients in comparison to healthy controls. However no significant results could be obtained when comparing tinnitus patients and patients with hearing loss but without tinnitus. Our results corroborate with these findings, as both the mean hearing loss, the range of the hearing

loss and hearing loss at the tinnitus frequency correlate with the functional connectivity between the left auditory cortex and the left parahippocampus based on the lagged phase coherence for the theta and alpha frequency band. That these functional connections are found within the theta and alpha frequency band fits with previous research demonstrating that theta and alpha oscillations are important for long-range communication (von Stein and Sarnthein, 2000).

However our results further elucidate that directionality in these functional connections seems to be important. While communication from the left parahippocampus to the left auditory is mediated by the mean hearing loss and the range of the hearing loss, communication from the left auditory cortex to the left parahippocampus is correlated to the hearing loss at the tinnitus frequency. A possible reason for this specific directional connectivity between the left auditory cortex and the left parahippocampus might be tonotopical representation (Kaas, 1997; Weinberg, 1997). While the auditory cortex is tonotopical organized, the parahippocampus has not been shown to be tonotopically structured. This could explain why hearing loss at the tinnitus frequency involves effective connectivity from the auditory cortex to the parahippocampus, hypothetically signaling from auditory cortex to parahippocampal which frequency-specific auditory input is missing. As there is no tonotopical representation in the parahippocampus the directional connectivity from the parahippocampus to the auditory cortex correlates only correlates with the mean hearing loss and range of the hearing loss. Thus it appears that the auditory cortex conveys what frequency is missing to the parahippocampus, while the parahippocampus transmits non-frequency-specific information to the auditory cortex, only related to the amount of hearing loss (i.e. filling in mechanism). This fits with the Bayesian model of tinnitus as it was suggested that the parahippocampus might fill in the missing auditory input by pulling the missing information from memory (De Ridder et al., 2014a).

According to these analyses it becomes clear that the parahippocampal area is a critical hub in tinnitus perception per se. But, importantly, it has recently been shown that functional connectivity between the parahippocampus and the subgenual anterior cingulate cortex in alpha determines how much distress and depression a patient feels associated to the phantom sound (De Ridder et al., 2011c; Joos et al., 2012; Vanneste et al., 2013; Vanneste and De Ridder, 2013; Vanneste et al., 2010a) and as mentioned, that functional connectivity between the parahippocampus and auditory cortex determines how loud the tinnitus is perceived (De Ridder et al., 2015b). It can be therefore hypothesized that the parahippocampal involvement might be related to the contextual influences that determine how loud and how stressful the tinnitus is perceived, in line with what has recently been proposed to be a major function for the parahippocampus, namely contextually influencing perception (Aminoff et al., 2013).

The lagged-phase synchronization between the left parahippocampal area and left auditory cortex related to the hearing loss is mainly in the theta frequency band. This fits with the thalamocortical dysrhythmia model, which suggests that the negative symptoms (i.e. hearing loss) are due to a decrease in incoming information processing, thereby permitting a slowing down of the oscillatory processing from alpha to theta (Llinas et al., 2005). It has been proposed that this theta could then act as a long range carrier wave (Freeman, 2003, 2005; Freeman and Rogers, 2002) on which the tinnitus information can be nested by means of high frequency oscillatory activity (De Ridder et al., 2014b). This notion has been confirmed by MEG studies which demonstrated increased coupled gamma - theta wave activity in tinnitus patients (Llinas et al., 2005; Llinas et al., 1999; Weisz et al., 2007) and recently demonstrated in EEG as well (De Ridder et al., 2015b), as well as on implanted electrodes overlying the auditory cortex in a tinnitus patient (De Ridder et al., 2011b).

Interestingly, our comparative date for no or minor hearing loss versus healthy controls or versus severe hearing loss are mainly lateralized to the left, whereas the correlation analysis of the hearing loss demonstrates bilateral parahippocampal activity changes. The comparative analysis looking at the difference between tinnitus with severe hearing loss and healthy controls demonstrates a difference with in the right parahippocampal area. Since no further analyses were performed to evaluate whether this left-sided temporal cortex lateralization is related to the side on which the tinnitus is perceived, no firm conclusions can be make about lateralization of brain activity and the tinnitus percept. In other words, this study cannot answer a longstanding question whether tinnitus is always related to a left-sided change as has been proposed before. An ongoing debate discusses whether tinnitus is always generated in the left or the contralateral auditory cortex (De Ridder, 2010). Previous functional MRI (Melcher et al., 2000; Smits et al., 2007), MEG (Llinas et al., 2005; Muhlnickel et al., 1998; Weisz et al., 2007) and EEG (van der Loo et al., 2009) studies suggest that the neural generator of the tinnitus is located in the contralateral auditory cortex (Smits et al., 2007) and inferior colliculus (Melcher et al., 2000), whereas most PET studies suggest tinnitus is always generated in the left auditory cortex (Arnold et al., 1996; Eichhammer et al., 2007). But some earlier positron emission tomography (PET) studies show increased metabolic activity in the auditory system of patients with tinnitus on the side contralateral to the side of perceived tinnitus (Lockwood et al., 1998). Other PET studies however report left-sided auditory cortex activation in predominantly left-sided tinnitus (Andersson et al., 2000) or irrespective of the tinnitus side (Arnold et al., 1996). Our current EEG data fit with the PET data to a certain extent.

Progress in finding a treatment for tinnitus has been hampered by the fact that tinnitus represents a highly heterogeneous condition (Schecklmann et al., 2012a, 2013). Hence, it was suggested that there might be different subtypes of tinnitus. Our research fits with this latter idea and shows that there might be at least two subtypes of tinnitus, one driven by the auditory cortex and one driven by the parahippocampus. Further studies should be performed evaluating these results with other functional imaging techniques, as well as by use of auditory cortex neuromodulation techniques to confirm this idea of subtyping. In view of the pathophysiological (De Ridder et al., 2011a), clinical (Moller, 1997) and treatment (De Ridder et al., 2007) analogies between deafferentation related tinnitus and deafferentation related pain, and the fact that synaptic and map plasticity changes are similar in all sensory domains (Buonomano and Merzenich, 1998; Donoghue, 1995; Feldman, 2009; Kaas, 1991), it would also be of interest to verify if this multiphase plasticity concept is valid for neuropathic pain as well to see whether this model could be universal.

A limitation of this study is that we choose 20 dB as a cut off for separating normal hearing from hearing loss. This is based on what is used in clinical practice. Possibly at a receptor or cellular level other amounts of hearing loss should be used as cut off measurements. Furthermore, we only tested hearing acuity in tinnitus patients by means of a standard pure tone audiometry limited to 8000 Hz. However, recent research has shown that tinnitus can occur in relationship with hearing loss at supra-clinical frequencies (above 8000 Hz) (Melcher et al., 2013). Future research should also include a high frequency audiogram as well as collect audiometrical data for healthy subjects. Controlling for hearing loss in healthy subjects will permit to explain why not all hearing-impaired individuals develop tinnitus and how they adapt differently to hearing loss than those that develop tinnitus. Another limitation of this study is the low resolution of the source localization inherently resulting from a limited number of sensors (19 electrodes) and a lack of subject-specific anatomical forward models. This is sufficient for source reconstruction but results in greater uncertainty in source localization and decreased anatomical precision, and thus the spatial precision of the present study is considerably lower than that of functional MRI. Nevertheless, the tomography sLORETA has received however considerable validation from studies combining LORETA with other more established localization methods, such as functional Magnetic Resonance Imaging (fMRI) (Mulert et al., 2004; Vitacco et al., 2002), structural MRI (Worrell et al., 2000), Positron Emission

Tomography (PET) (Dierks et al., 2000; Pizzagalli et al., 2004; Zumsteg et al., 2005) and was used in previous studies to detect for example activity in the auditory cortex (Vanneste et al., 2010b, 2011a; Zaehle et al., 2007). Further sLORETA validation has been based on accepting as ground truth the localization findings obtained from invasive, implanted depth electrodes, in which case there are several studies in epilepsy (Zumsteg et al., 2006a,c) and cognitive ERPs (Volpe et al., 2007). It is worth emphasizing that deep structures such as the anterior cingulate cortex (Pizzagalli et al., 2001), and mesial temporal lobes (Zumsteg et al., 2006b) can be correctly localized with these methods. The involvement of the parahippocampus was already illustrated in previous research using low density EEG and was confirmed subsequently by PET and MRI suggesting the reliabilities of our findings. Our data further illustrate that source reconstruction can clearly make a difference between the hippocampus and the parahippocampus as the lagged phase synchronization is relatively small. However, further research could improve spatial precision and accuracy could be achieved using high-density EEG (e.g., 128 or 256 electrodes) and subject-specific head models, and MEG recordings. In addition, lagged phase coherence analysis requires the selection of regions of interest based on a priori knowledge, or by means of heuristic procedures (i.e. only analyze functional connectivity between areas with altered activity)(David et al., 2002; Kujala et al., 2008). The impossibility of a purely data driven approach (i.e. whole brain connectivity analysis independent of regions of interest) automatically implies a theoretically funded approach is required, thereby selecting regions of interest. This can be seen as a weakness but unfortunately is inherent to the technique (Babiloni et al., 2005). Future research might also take into account the memory function, as it is possible that memory function is involved as a "filling in" mechanism.

In conclusion, our results show that there might be different tinnitus generating mechanisms, based on the amount of hearing loss. It was demonstrated that the parahippocampal area becomes involved in tinnitus based on hearing loss. This is in accordance with a recently proposed model that states a theoretical multiphase compensation mechanism at a cortical level has been hypothesized linking auditory deafferentation to tinnitus (De Ridder et al., 2012).

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Supplementary data

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