NeuroImage 297 (2024) 120713

Contents lists available at ScienceDirect

NeuroImage

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

Switching tinnitus on or off: An initial investigation into the role of the pregenual and rostral to dorsal anterior cingulate cortices

Sven Vanneste [a,b,c,1,*], Gabriel Byczynski [a,b], Thierry Verplancke [c], Jan Ost [c], Jae-Jin Song [d,e], Dirk De Ridder [c,f]

[a] Lab for Clinical & Integrative Neuroscience, School of Psychology, Trinity College Dublin, College Green 2, Dublin, Ireland
[b] Global Brain Health Institute & Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland
[c] Brai3n, Ghent, Belgium
[d] Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, the Republic of Korea
[e] Sensory Organ Research Institute, Seoul National University Medical Research Center, Seoul, the Republic of Korea
[f] Unit of Neurosurgery, Department of Surgical Sciences, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand

ARTICLE INFO

Keywords:
Tinnitus
Distress
Pregenual anterior cingulate cortex
Dorsal anterior cingulate cortex
On/off switch

ABSTRACT

Research indicates that hearing loss significantly contributes to tinnitus, but it alone does not fully explain its occurrence, as many people with hearing loss do not experience tinnitus. To identify a secondary factor for tinnitus generation, we examined a unique dataset of individuals with intermittent chronic tinnitus, who experience fluctuating periods of tinnitus. EEGs of healthy controls were compared to EEGs of participants who reported perceiving tinnitus on certain days, but no tinnitus on other days.. The EEG data revealed that tinnitus onset is associated with increased theta activity in the pregenual anterior cingulate cortex and decreased theta functional connectivity between the pregenual anterior cingulate cortex and the auditory cortex. Additionally, there is increased alpha effective connectivity from the dorsal anterior cingulate cortex to the pregenual anterior cingulate cortex. When tinnitus is not perceived, differences from healthy controls include increased alpha activity in the pregenual anterior cingulate cortex and heightened alpha connectivity between the pregenual anterior cingulate cortex and auditory cortex. This suggests that tinnitus is triggered by a switch involving increased theta activity in the pregenual anterior cingulate cortex and decreased theta connectivity between the pregenual anterior cingulate cortex and auditory cortex, leading to increased theta-gamma cross-frequency coupling, which correlates with tinnitus loudness. Increased alpha activity in the dorsal anterior cingulate cortex correlates with distress. Conversely, increased alpha activity in the pregenual anterior cingulate cortex can transiently suppress the phantom sound by enhancing theta connectivity to the auditory cortex. This mechanism parallels chronic neuropathic pain and suggests potential treatments for tinnitus by promoting alpha activity in the pregenual anterior cingulate cortex and reducing alpha activity in the dorsal anterior cingulate cortex through pharmacological or neuromodulatory approaches.

1. Introduction

Tinnitus is the perception of a phantom sound that affects more than 1 in 7 adults (Biswas et al., 2022), and in 1 in 5 of those affected it becomes a disorder (Axelsson and Ringdahl, 1989; Bhatt et al., 2017; De Ridder et al., 2021b). The lack of knowledge of its mechanisms seriously hinders the quest for viable treatments. A risk factor for tinnitus is hearing loss (Biswas et al., 2023), which drives neuroplasticity changes, including increases in the spontaneous neural firing and/or synchrony in the auditory cortex in response to reduced input (Sedley, 2019). Although hearing loss contributes to tinnitus, it is not sufficient to explain the development of tinnitus as most people with hearing loss do not have tinnitus. Even though the prevalence of tinnitus increases with age and is linked to age-related presbycusis, only 1 in 4 people over 65 years old perceive tinnitus (Jarach et al., 2022). Thus, a second factor needs to be present to turn hearing loss into tinnitus.

* Corresponding author at: Lab for Clinical & Integrative Neuroscience, School of Psychology, Trinity College Dublin, College Green 2, Dublin, Ireland.
E-mail address: sven.vanneste@tcd.ie (S. Vanneste).
[1] website: https://www.lab-clint.org.

https://doi.org/10.1016/j.neuroimage.2024.120713
Received 14 December 2023; Received in revised form 25 June 2024; Accepted 26 June 2024
Available online 27 June 2024

In order to properly prevent and treat this devastating hearing disorder and its effects on health, it is necessary to identify this second risk factor and understand its neurophysiological effect. Recent studies have established that emotional exhaustion and long-term stress are predictors of hearing disorders, including tinnitus (Hasson et al., 2011; Jarach et al., 2022). About 52 % of individuals noted an aggravation of tinnitus symptoms when experiencing emotional stress (Mazurek et al., 2015) and fluctuations in emotional states over time are associated with a less favorable time course of the tinnitus loudness (Probst et al., 2016). Functional and electroencephalographic brain imaging studies have further shown an aberrant link between limbic (involved in emotions) and auditory structures in tinnitus patients (Leaver et al., 2011; Vanneste et al., 2014), where the subgenual and rostral to dorsal anterior cingulate cortex have a specific role in tinnitus-related distress (Vanneste et al., 2014, 2010a). More specifically, tinnitus-related distress is related to alpha and beta activity in the rostral to dorsal anterior cingulate cortex, and the amount of tinnitus-related distress is associated with an alpha network consisting of the amygdala-anterior cingulate cortex-insula-parahippocampal area (Vanneste et al., 2014, 2010a). Animal studies have further demonstrated that stress influenced auditory cortex neural activity, resulting in an amplification of sound-evoked responses (Ma et al., 2015).

Independent of hearing loss, research has proposed that tinnitus is related to a change in the pregenual anterior cingulate cortex that corresponds to increased activity in the auditory cortex (Vanneste et al., 2019a) and correlates with the percentage of time that the tinnitus is dominantly present throughout the day (Song et al., 2015). The pregenual anterior cingulate cortex plays a pivotal role as a top-down putative central gatekeeper that evaluates the relevance and affective meaning of sensory stimuli and controls information via a descending inhibitory pathway to the thalamic reticular nucleus (Leaver et al., 2011). The thalamic reticular nucleus modulates this information flow between the thalamus and the auditory cortex by inhibiting specific thalamic neurons in a highly selective and frequency-specific manner (Rauschecker et al., 2015; Vanneste et al., 2019a; Yu et al., 2009). In tinnitus patients this top-down gating mechanism, also known as the noise-canceling mechanism (Leaver et al., 2011; Rauschecker et al., 2010; Song et al., 2015), seems to be deficient resulting in a reduced inhibitory signal transmission to the auditory cortex (Vanneste et al., 2019a). This reduced signal transmission from the pregenual anterior cingulate cortex as reflected at the theta frequency band is associated with increased activity in the auditory cortex in the theta and gamma frequency bands that is phase-amplitude coupled (Vanneste et al., 2019a). The gamma activity in the auditory cortex goes together with how loud tinnitus patients perceive tinnitus (De Ridder et al., 2015a; van der Loo et al., 2009; Weisz et al., 2007, 2005). It is interesting to note that people with hearing loss who do not perceive tinnitus are characterized by increased alpha activity in the pregenual anterior cingulate cortex as well as increased phase coherence between the pregenual anterior cingulate cortex and the auditory cortex for the alpha frequency band (Vanneste et al., 2019a).

More generally, the pregenual anterior cingulate cortex is a key brain structure of the corticolimbic circuit and responds in a maladaptive way to chronic stress (McEwen et al., 2016). The pregenual anterior cingulate cortex is known to be affected by afferent and efferent projections from other brain areas including the dorsal anterior cingulate cortex, amygdala, and hippocampus which together form a network present in stress-related illness (McEwen et al., 2016; Misquitta et al., 2021). In chronic stress, the pregenual anterior cingulate cortex undergoes changes, leading to an imbalance in stress-related neurochemicals such as cortisol and serotonin (De Ridder et al., 2021a; Lucassen et al., 2014). Furthermore, the pregenual anterior cingulate cortex endures a volumetric reduction as a consequence of chronic stress that is due to a reorganization in synaptic and dendritic density (Misquitta et al., 2021). This atrophy is reversible, i.e. when the stress subsides the volumetric reduction normalizes again (Soares et al., 2012).

Although distress has long been identified as a co-morbidity of tinnitus (Mazurek et al., 2023), it is imperative to delve into whether distress might serve also as a trigger for the onset of tinnitus and what the neurophysiological mechanisms are that underlie this trigger. Here we test the hypothesis whether the pregenual anterior cingulate cortex plays an important role in the onset of tinnitus. We hypothesize that the dorsal anterior cingulate cortex that regulates distress in alpha can slow-down activity in the pregenual anterior cingulate cortex reflected by increased theta activity when participants perceive tinnitus. Secondary, the pregenual anterior cingulate cortex as a top-down inhibitory central gatekeeper could trigger the tinnitus percept in the auditory cortex which would be reflected by theta and gamma activity. For this purpose, we analyze a unique dataset consisting of patients diagnosed with chronic tinnitus. These patients intermittently report perceiving tinnitus on certain days, while on other days, they do not experience any tinnitus at all. We further hypothesize that when these patients do not perceive tinnitus, this is characterized by alpha activity in the pregenual anterior cingulate cortex that induces an inhibitory response to the auditory cortex. To test our hypothesis, we collected electrophysiological data (i.e., electroencephalography) in participants who perceive tinnitus on some days, but do not perceive tinnitus on other days. The EEGs are complemented by VAS loudness scores and tinnitus questionnaire scores, the latter evaluating tinnitus-related distress. This unique position provides us with the opportunity to gain a better understanding for the role of distress in the tinnitus percept via the pregenual anterior cingulate cortex.

2. Methods and materials

2.1. Subjects

A total of 9 participants (age: 57.42 ± 4.56 years; males: 3; females: 6) were recruited for this study. They reported perceiving tinnitus on certain days, while on other days do not experience any tinnitus at all. Tinnitus patients were recruited from the Brai3n clinic (www.brai3n.com) after being screened by two tinnitus specialist/medical practitioner and were asked if they would be willing to participate in a study. All participants underwent an audiological assessment for the extent of hearing loss (dB HL) per the British Society of Audiology procedures at 0.125, 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz (British Society of Audiology, 2008). Individuals with pulsatile tinnitus, Meniere'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 maximize the sample homogeneity. All participants gave their written, informed consent per the approved guidelines. The study was in accordance with the ethical standards of the Helsinki declaration (1964) and was approved by the institutional ethics committee of the University Hospital Antwerp (UZA OGA85).

All tinnitus participants 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) and tinnitus duration (see Table 1). A visual analogue scale for loudness ('How loud is your tinnitus?': 0 = no tinnitus and 100 = as

Table 1
Tinnitus characteristics.

Tinnitus feature	
Tinnitus lateralization	
Left ear	2
Right ear	2
Bilateral	5
Tinnitus sound	
Pure tone	2
Noise like	7
Tinnitus duration	4.61 years (3 to 5.5 years)

loud as imaginable') was assessed to measure the subjective loudness. We assessed tinnitus-related distress using the Dutch translation of the mini Tinnitus Questionnaire (mini-TQ) (Vanneste et al., 2011a). This scale is a well-established measure for the assessment of a broad spectrum of tinnitus-related psychological complaints that measures emotional and cognitive distress, intrusiveness, auditory perceptual difficulties, sleep disturbances, and somatic complaints. The TQ score can be computed to measure the general level of psychological and psychosomatic distress. In studies conducted across several countries, this measure has been shown to be a reliable and valid instrument (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 24) was computed according to standard criteria published in previous work (Hiller and Goebel, 1992; Hiller et al., 1994; Meeus et al., 2007). We did not measure tinnitus distress during the 'off-state' for two reasons, the first being that we wished to avoid the triggering or onset of tinnitus as a result of probing for percept quality, and second, because the reporting of tinnitus during the off-state has not been established as a reliable measure of tinnitus distress (as it would vary based on recall ability, recency of onset/offset, and likely be compounded by distress). Thus, this would be an interesting topic for future work, but was not pursued here.

In addition, as a control group, we include nine participants (age: 56.02 ± 3.71 years; males: 3; females: 6) who reported having no tinnitus. The participants were matched for age, gender and hearing thresholds (including comparable hearing loss). The control group reported no history of neurological or neuropsychiatric disorders.

2.2. EEG collection and processing

1. Data collection

EEG recordings were obtained in a fully lit room with each participant sitting upright on a small but comfortable chair. People were given between 30 and 45 min to get acquainted with the room. During this time, the study nurse would prep the participant and make sure each individual was feeling comfortable. The actual recording lasted approximately five minutes, consistent with recommendations from *On the Standardization of M/EEG procedures in tinnitus research* (https://tinnet.tinnitusresearch.net/index.php/recommendations), and consistent with other studies which use 5 min resting states and which indicate that neural connectivity stabilizes in acquisition times as short as 5 min. Tinnitus patients were measured twice (once during the on-state, and once during the off-state), while control participants were measured once. Patients were recorded when they perceived their tinnitus and were asked to contact us when they did not perceive their tinnitus. For each patient, this varied from two days up to 12 days before they contacted us.

The EEG was sampled using Mitsar-201 amplifiers (NovaTech http://www.novatecheeg.com/) with 19 Ag/AgCl electrodes placed according to the standard 10–20 International placement. Impedances were checked to remain below 5 kΩ. Data were collected eyes-closed (sampling rate = 500 Hz, band passed 0.15–200 Hz). Participants were instructed not to drink alcohol 24 h prior to EEG recording or caffeinated beverages one hour before recording to avoid alcohol- or caffeine-induced changes in the EEG stream (Logan et al., 2002; Siepmann and Kirch, 2002; Volkow et al., 2000). The alertness of participants was checked by monitoring both slowing of the alpha rhythm and appearance of spindles in the EEG stream to prevent possible enhancement of the theta power due to drowsiness during recording (Moazami-Goudarzi et al., 2010). 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 movements, teeth clenching, body movement, or ECG artifact were removed from the stream of the EEG. An artifact was defined as an EEG characteristic that differs from signals generated by activity in the brain. 1) Some artifacts are known to be in a limited frequency range, e.g., above some frequency. These were removed by frequency filtering. 2) Some artifacts consist of discrete frequencies such as 50 Hz or its harmonics. These were removed by notch filtering. 3) Some artifacts are limited to a certain time range, e.g., in the case of eye blinks. These artifacts were recognized by visual inspection and these time intervals were discarded. 4) Some artifacts originate from one or a few distinct sources or a limited volume of space so that the artifact topography is a superposition of characteristic topographies (equivalently, the artifact is limited to a subspace of the signal space). We removed these artifacts by determining the characteristic topographies (equivalently, the artifact subspace) so that the remaining signals do not contain anything from the artifact subspace. 5) Artifacts and true brain signals that can be assumed to be sufficiently independent can be removed by independent component analysis. 6) Some artifacts are characterized by a particular temporal pattern such as exponential decay. We removed these artifacts by modeling the artifact and fitting its parameters to the data and then removing the artifact.

Average Fourier cross-spectral matrices were computed for frequency bands delta (2–3.5 Hz), theta (4–7.5 Hz), alpha (8–12 Hz), beta (13–30 Hz), and gamma (30.5–44 Hz). No differences in the length of the EEG was observed from artefact rejection between the control and tinnitus groups during on-state ($U = 0.041$, $p = .85$) or off-state ($U = 0.032$, $p = .91$).

2. 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. Details about the regularization parameters can be found in transformation (Pascual-Marqui, 2002). 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 cingulate cortex) MNI-152 space 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.

3. Region of interest analysis

The log-transformed electric current densities were calculated for the regions of interest (ROIs) for the different frequency bands: theta (4–7.5 Hz), alpha (8–12 Hz) and gamma (30.5–44 Hz). The ROIs in the present study are dorsal anterior cingulate cortex, the pregenual anterior cingulate cortex. We do not differentiate between left and right cingulate due to their proximity to the midline. Due to volume conduction, laterality is harder to differentiate for areas close to the midline. For the primary auditory cortex (defined here as Heschl's gyrus), we only include the left side as the whole brain analysis only showed left-sided activity. The selection of these regions of interest and frequency band was based on our hypothesis as introduced in the introduction (a priori) and confirmed by the comparison of activity between the tinnitus groups with hearing loss (a posteriori).

4. Lagged phase coherence

Coherence and phase synchronization between time series corresponding to different spatial locations are usually interpreted as indicators of "connectivity". However, any measure of dependence is highly contaminated with an instantaneous, non-physiological contribution due to volume conduction (Pascual-Marqui, 2007b). 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 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), 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), alpha (8–12 Hz), beta (13–30 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. Regions of interest selected were the dorsal anterior cingulate cortex, pregenual anterior cingulate cortex and the left auditory cortex.

5. Granger causality using isolated effective coherence

Granger causality reflects the strength of effective connectivity from one region to another (i.e. causal interactions, where extracted activity of one area exhibits causal influences of one neural element over 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 a directional functional connectivity. Granger causality is based on formulating a multivariate autoregressive model and calculating the corresponding partial coherences after setting all irrelevant connections to zero. We decided to use Granger causality as it can be directly applied to any given time series to detect the coupling among empirically sampled neuronal systems (Friston et al., 2013). This can provide insights into the dynamical behavior of a system in spontaneously active 'resting' states (Friston et al., 2013). Granger causality is accepted because there is no temporal lag between the responses recorded and their underlying causes and because the data can be sampled at fast timescales. The advantages of Granger causality in furnishing frequency-dependent and multivariate measures have been clearly demonstrated in previous electrophysiology research (Barrett et al., 2012; Bosman et al., 2012). Here we used an extended version of the Granger causality using isolated effective coherence.

All technical details can be found in Pascual-Marqui et al. (2014a), Stokes and Purdon (2017). The partial directed coherence (PDC) is a measure designed to quantify direct connections that are not confounded by indirect paths, their directionality and spectral characteristics (Baccala and Sameshima, 2001). Schelter and colleagues pointed out that the normalization used in PDC, i.e. the denominator in the PDC formula (see below) contains all influences from a source node to all other (receiving) nodes, and as a consequence, the PDC decreases in the presence of many nodes, even if the relationship between source and target nodes remains unchanged (Schelter et al., 2009). The solution to this problem was given in the form of a renormalization of the PDC, using the statistical variance of the strength of the connection. Rather the aiming at a re-normalization of the PDC, Pascual-Marqui and coworkers reformulate the problem from scratch, estimating the partial coherence under a multivariate auto-regressive model, followed by setting all irrelevant associations to zero, other than the particular directional association of interest (Pascual-Marqui et al., 2014a, 2014b, 2011). This procedure is akin to Pearl's "surgical intervention" for studying causality (Pearl, 2000). This approach gives the isolated effective coherence (iCoh).

In this study, we look at the effective connectivity between the pregenual anterior cingulate cortex and dorsal anterior cingulate cortex, at the theta and alpha frequency band respectively. We selected these frequency bands based on the introduction (a priori).

6. Cross-frequency coupling

Theta-gamma coupling (e.g., by nesting) is proposed to be an effective manner of communication between cortically distant areas (Canolty et al., 2006). To verify whether this theta–gamma nesting was present, it was calculated for the left auditory cortex using phase–amplitude cross-frequency coupling. Phase–amplitude was chosen over power–-power cross-frequency coupling as the former has been shown to reflect a physiological mechanism for effective communication in the human brain (Canolty et al., 2006). Nesting was computed by first obtaining the time-series for the x, y, and z components of the sLORETA current for the voxel of each ROI. These are the time-series of the electrical current in the three orthogonal directions in space. Next, these were filtered in the theta (4–7.5 Hz) and gamma (30.5–44 Hz) frequency band-pass regions. In each frequency band and for each ROI, a principal component analysis for the overall x, y, z component was computed, and the first component was retained for the theta and gamma bands. The Hilbert transform was then computed on the gamma component and the signal envelope retained. Finally, the Pearson correlation between the theta component and the envelope of the gamma envelope was computed for each individual.

2.3. Statistical analyses

Primary hypothesis driven analysis.

1. Sensor space analysis

A group wise comparison was conducted where the power spectra of the different groups were compared with both independent and dependent samples *t*-test for each frequency point.

2. 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). These whole brain comparisons were performed by sLORETA through multiple voxel-by-voxel comparisons using a logarithm of *F*-ratio. The significance threshold for all tests was based on a permutation test with 5000 permutations. Comparisons were made between the tinnitus and non-tinnitus subject groups.

3. Region of interest

To compare participants when perceiving tinnitus versus not perceiving tinnitus we applied the Wilcoxon Signed Ranks test. To compare tinnitus patients in the on-state and off-state with a control group we applied the Mann-Whitney *U* test.

In addition, Spearman rho correlations were calculated for both the gamma frequency band for the log-transformed current density for left auditory cortex and tinnitus loudness in tinnitus subjects who were perceiving tinnitus. A similar analysis was applied for the alpha frequency band for the log-transformed current density for dorsal anterior cingulate cortex and distress for subjects who were perceiving tinnitus.

Secondary exploratory analysis.

1. Lagged phase coherence

Lagged phase coherence contrasts were calculated for the different frequency bands (delta, theta, alpha, beta, and gamma) between tinnitus and non-tinnitus subjects. 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).

2. Granger causality

To compare participants when perceiving tinnitus versus not perceiving tinnitus we applied the Wilcoxon Signed Ranks test to look at the cross-frequency effective connectivity to compare from alpha frequency at the dorsal anterior cingulate cortex to the theta frequency for the pregenual anterior cingulate cortex. We also compared the cross-frequency effective connectivity from the theta frequency for the pregenual anterior cingulate cortex to alpha frequency at the dorsal anterior cingulate cortex.

To compare participants when perceiving tinnitus and not perceiving tinnitus with a control group we applied the Mann-Whitney *U* test.

3. Phase-amplitude coupling

We performed the Wilcoxon Signed Ranks test to compare participants when perceiving tinnitus versus not perceiving tinnitus for the phase-amplitude coupling for theta-gamma coupling for left auditory cortex.

3. Results

3.1. Behavioral assessment

The average loudness ($M = 4.56$, $Sd = 1.51$) and distress ($M = 13.56$, $Sd = 4.77$) was computed when participants perceive tinnitus. There was no significant difference between controls and intermittent tinnitus patients for hearing loss for the left and right ear ($F = 0.65$, $p = .88$; see Fig. 1). It should be noted that both groups did display a level of hearing loss. Thus, the use of 'control' in this paper will refer to a group without tinnitus, but with which there is evident hearing loss comparable to the tinnitus group (hearing loss, no-tinnitus). This further reduces the scope of our findings as being strictly tinnitus-related, and not as a result of hearing loss when comparing groups. More information about the tinnitus characteristics can be found in Table 1.

3.2. Sensor space analysis

Comparing participants when they perceive tinnitus from when they do not perceive tinnitus, significant increased theta in the mid-frontal areas, increased alpha power in mainly frontal areas as well as increased gamma power in left temporal areas during tinnitus perception ($F = 4.27$, $p < .05$). No effect was obtained for the delta and beta band. See top Fig. 2.

Comparing participants when they perceive tinnitus from control subjects, significant increased theta was observed in the mid-frontal area as well as increased gamma power in left temporal areas in the participants perceiving tinnitus ($F = 3.91$, $p < .05$).. No effect was obtained for the delta, alpha and beta bands. See bottom left Fig. 2.

Furthermore, comparing participants when they do not perceive tinnitus from to controls, a significant increase was obtained in the mid-frontal areas for tinnitus participants during the off-state for the alpha frequency band ($F = 4.15$, $p < .05$).. No effect was obtained for the delta, theta, beta and gamma bands. See bottom right Fig. 2.

3.3. Whole brain analysis

A comparison within shows a significant effect for the theta ($F = 4.51$, $p < .05$), alpha ($F = 4.36$, $p < .05$) and gamma frequency bands ($F = 4.59$, $p < .05$). For the theta frequency band, increased activity was identified in the pregenual anterior cingulate cortex extending into the ventral medial prefrontal cortex. For alpha, increased activity was found in the dorsal anterior cingulate cortex extending into the dorsal medial prefrontal cortex during the perception of the tinnitus. For the gamma frequency band, increased activity was identified in the left auditory cortex as well as the lateral inferior parietal lobule during the perception of tinnitus. No significant effects were found for the delta and beta frequency bands. See top Fig. 3.

A comparison between participants while perceiving tinnitus versus a control group revealed increased activity for both the theta ($F = 4.02$, $p < .05$) and gamma ($F = 3.88$, $p < .05$) frequency bands in the tinnitus patients. More precisely, for the theta frequency band, increased activity was identified in the pregenual anterior cingulate cortex extending into the ventral medial prefrontal cortex and for the gamma frequency band

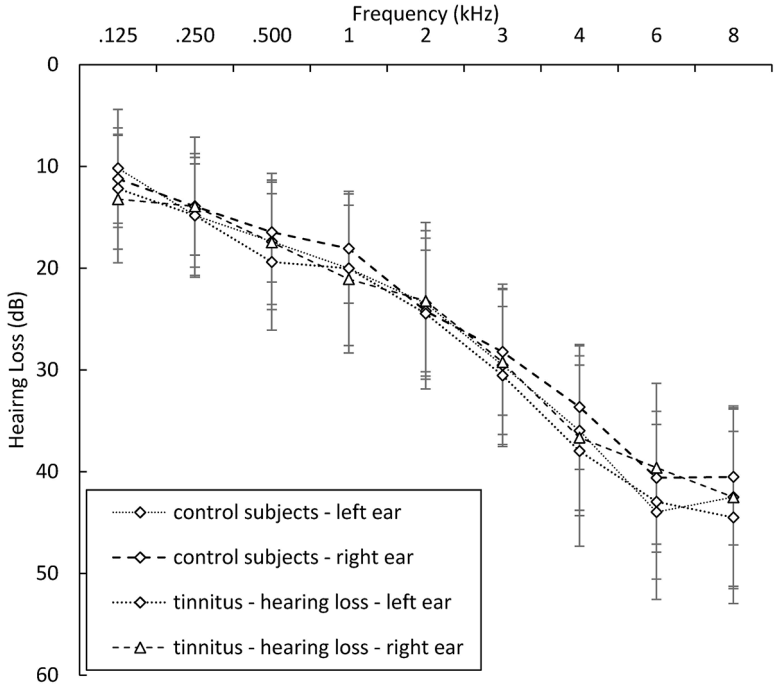

Fig. 1. The average audiogram for both subjects with and without tinnitus showed no difference between the two groups for both the left and right ear.

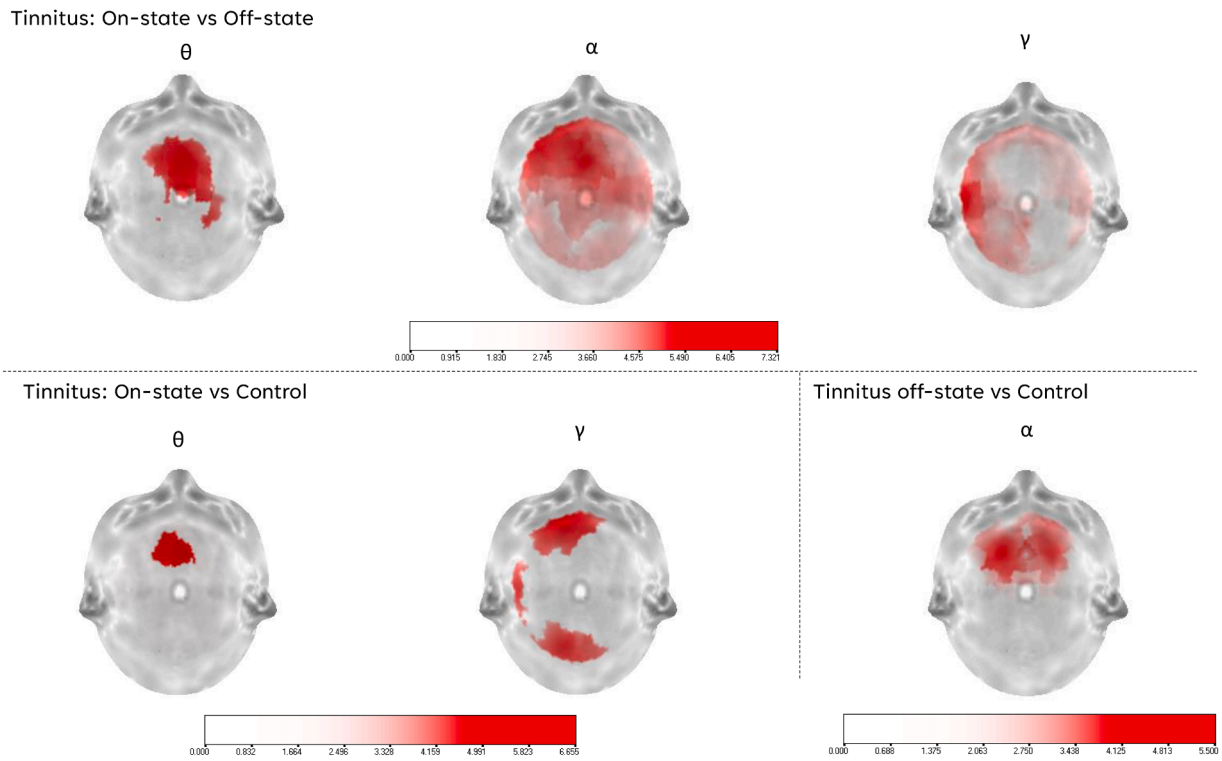

Fig. 2. (top panel) Comparing participants when they perceive tinnitus from when they do not perceive tinnitus shows a significant increased theta in the mid-frontal areas, increased alpha power in mainly frontal areas as well as increased gamma power in left temporal areas during tinnitus perception (bottom left) Comparing participants when they perceive tinnitus from control subjects reveals increased theta in the mid-frontal area as well as increased gamma power in left temporal areas. (bottom right). Comparing participants when they do not perceive tinnitus from controls shows increased mid-frontal areas for tinnitus participant during the off-state in alpha.

increased activity was found in the auditory cortex extending into the lateral anterior mid-temporal area (see bottom left Fig. 3). No significant effects were obtained for the delta, alpha and beta frequency bands.

A comparison between participants during not perceiving tinnitus percept versus a control group without tinnitus, revealed increased activity for the alpha frequency band in the pregenual anterior cingulate cortex extending into the ventral medial prefrontal cortex in participants during not perceiving tinnitus percept ($F = 5.60$, $p < .05$; see bottom right Fig. 3). No significant effects were obtained for the delta, theta, beta and gamma frequency bands.

3.4. Region of interest analysis

In the pregenual anterior cingulate cortex, significantly increased log-transformed theta current density was identified in tinnitus patients during the perception of tinnitus ($M = 0.19$, $Sd = 0.053$) in comparison to not perceiving tinnitus ($M = 0.12$, $Sd = 0.055$; $W = 2.55$; $p = .011$) as well as with control subjects ($M = 0.13$, $Sd = 0.059$; $U = 6.18$, $p = .024$). A comparison between not perceiving tinnitus and control subjects revealed no significant effect ($U = 0.20$, $p = .66$). See Fig. 4a for an overview.

In the pregenual anterior cingulate cortex significantly increased log-transformed alpha current density was identified in tinnitus patients during not perceiving tinnitus ($M = 0.27$, $Sd = 0.097$) in comparison to perceiving tinnitus ($M = 0.12$, $Sd = 0.079$; $W = 2.55$; $p = .011$) and control subjects ($M = 0.16$, $Sd = 0.078$; $U = 2.43$, $p = .014$). A comparison between perceiving tinnitus and control subjects revealed no significant effect ($U = 0.31$, $p = .34$). See Fig. 4b for an overview.

In the dorsal anterior cingulate cortex, a significantly increased log-transformed alpha current density was identified during the perception of tinnitus ($M = 0.24$, $Sd = 0.13$) in comparison to not perceiving tinnitus ($M = 0.14$, $Sd = 0.069$; $W = 2.07$; $p = .038$) and control subjects ($M = 0.14$, $Sd = 0.064$; $U = 2.07$, $p = .040$). A comparison between not perceiving tinnitus and control subjects revealed no significant effect ($U = 0.90$, $p = .93$). See Fig. 4c for an overview.

For the auditory cortex for the theta frequency band, no significant effect was obtained when comparing participants during tinnitus perception ($M = 0.16$, $Sd = 0.11$) with not perceiving tinnitus ($M = 0.23$, $Sd = 0.13$; $W = 1.13$; $p = .26$) or controls ($M = 0.26$, $Sd = 0.19$; $U = 0.10$ $p = .11$). A comparison between perceiving tinnitus and control subjects revealed no significant effect ($U = 0.90$, $p = .93$). See Fig. 4d for an overview.

For the auditory cortex for the gamma frequency band, a significant effect was found when comparing during tinnitus perception ($M = 0.045$, $Sd = 0.021$) no tinnitus perception ($M = 0.018$, $Sd = 0.01$; $W = 2.43$; $p = .015$) or controls ($M = 0.035$, $Sd = 0.012$; $U = 2.34$ $p = .019$). A comparison between perceiving tinnitus and control subjects revealed no significant effect ($U = 1.28$, $p = .22$). See Fig. 4e for an overview.

3.5. Correlations

A spearman correlation between log-transformed current density for the auditory cortex at the gamma frequency band and loudness revealed a significant positive association ($\rho = 0.73$, $p = .027$), indicating that louder tinnitus was associated with higher current density at gamma frequency, or vice versa (see Fig. 5a). In addition, a spearman correlation between log-transformed current density for the rostral to dorsal anterior cingulate cortex at the alpha frequency band and distress revealed a significant positive association ($\rho = 0.79$, $p = .011$). This latter finding indicated that the more distress tinnitus patients perceived, the more current density at alpha frequency was measured, or vice versa. (see Fig. 5b).

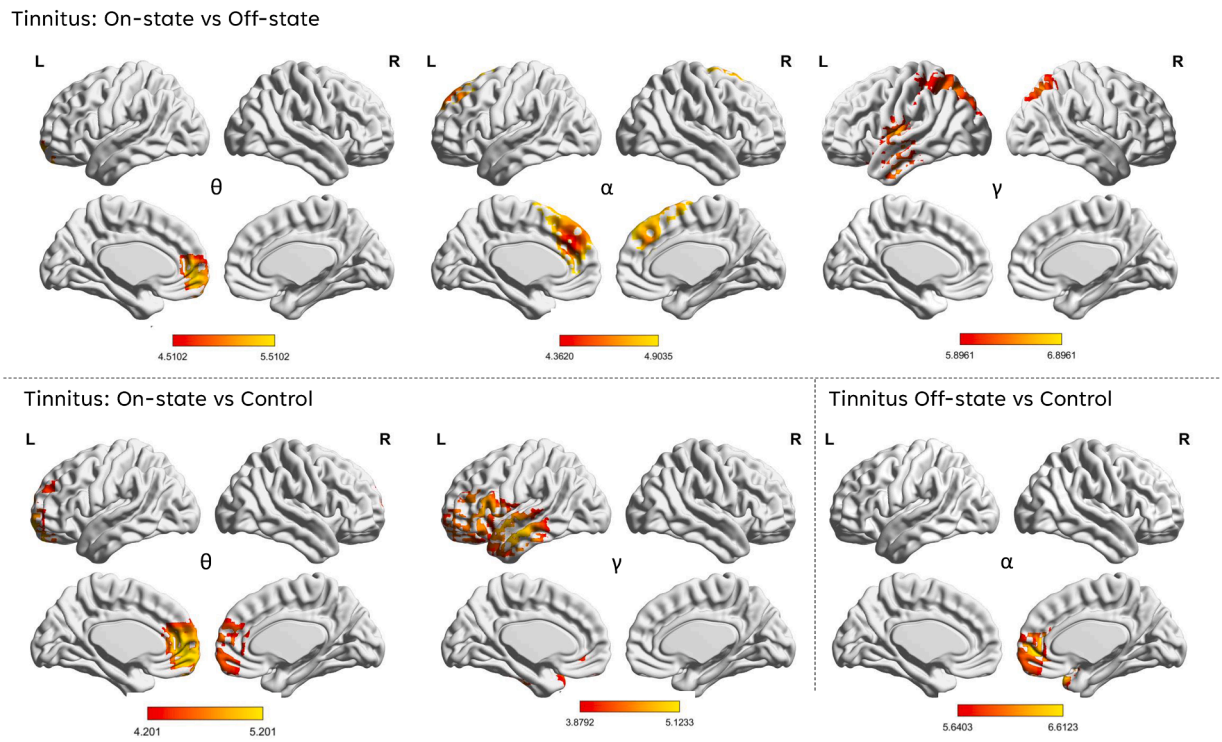

Fig. 3. (top panel) When participants perceive tinnitus show a significant effect for the theta, alpha and gamma frequency band in comparison to not perceiving tinnitus. For theta frequency band increased activity was demonstrated in the pregenual anterior cingulate cortex extending into the ventral medial prefrontal cortex. For the alpha increased activity in the dorsal anterior cingulate cortex extending into the dorsal medial prefrontal cortex was obtained. For the gamma frequency band increased activity was demonstrated in the left auditory cortex as well as the partial lobe during the perception of the tinnitus. (lower panel, left) A comparison between participants during perceiving tinnitus percept versus a control group, revealed increased activity for both the theta and gamma frequency bands for the participant perceiving tinnitus. For the theta frequency band increased activity was identified in the pregenual anterior cingulate cortex extending into the ventral medial prefrontal cortex. For the gamma frequency band increased activity was revealed in the auditory cortex extending in the into the temporal pole. (lower panel, right). A comparison between participants during not perceiving tinnitus percept versus a control group, revealed increased activity in the pregenual anterior cingulate cortex extending into the ventral medial prefrontal cortex in participants during not perceiving tinnitus percept for the alpha frequency band.

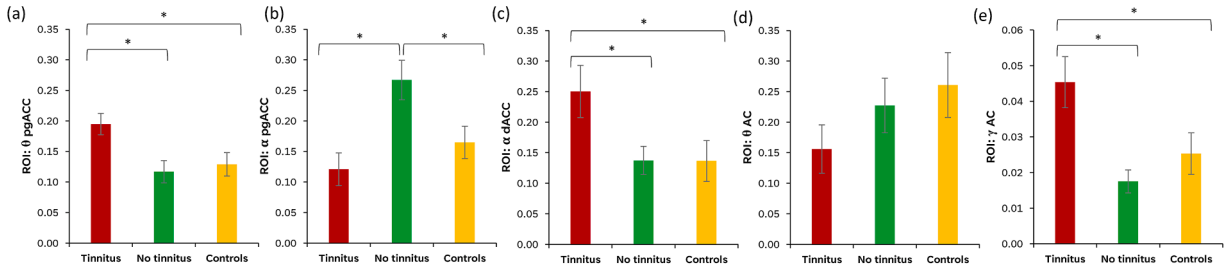

Fig. 4. (a) A region of interest revealed that the pregenual anterior cingulate cortex (pgACC) at the theta frequency band, had significant increased log-transformed current density during the perception of tinnitus in comparison to not perceiving tinnitus and controls. (b) For the pregenual anterior cingulate cortex at the alpha frequency band, significant increased log-transformed current density was demonstrated during not perceiving tinnitus (in comparison to perceiving tinnitus and control subjects. (c) The dorsal anterior cingulate cortex (dACC) at the alpha frequency band, we revealed a significant increased log-transformed current density was identified during the perception of tinnitus in comparison to not perceiving tinnitus and controls subject. (d) For the auditory cortex (AC) for the theta frequency band, no significant effect was found when comparing during perceiving tinnitus with not perceiving tinnitus or controls. (e) For the auditory cortex for the gamma frequency band, a significant effect was yielded when comparing during perceiving tinnitus (with not perceiving tinnitus or controls.

3.6. Lagged phase coherence

When comparing tinnitus participants during tinnitus perception and no tinnitus perception, a significantly reduced functional connectivity was identified for the theta frequency band between the pregenual anterior cingulate cortex and auditory cortex in patients perceiving tinnitus ($F = 4.11, p < .05$). No significant effect was found between the rostral to dorsal anterior cingulate cortex and both the auditory cortex and the pregenual anterior cingulate cortex. No significant effects were obtained when comparing tinnitus and non-tinnitus subjects for the delta, alpha, beta, and gamma frequency bands. See top Fig. 6.

When comparing tinnitus participants during tinnitus perception and control subjects, significantly reduced functional connectivity was identified for the theta frequency band between the pregenual anterior cingulate cortex and auditory cortex during tinnitus perception ($F = 4.09, p < .05$). No effect was obtained between the rostral to dorsal anterior cingulate cortex and both the auditory cortex and the pregenual anterior cingulate cortex. No significant effects were obtained when comparing tinnitus and non-tinnitus subjects for the delta, alpha, beta, and gamma frequency bands. See middle Fig. 6.

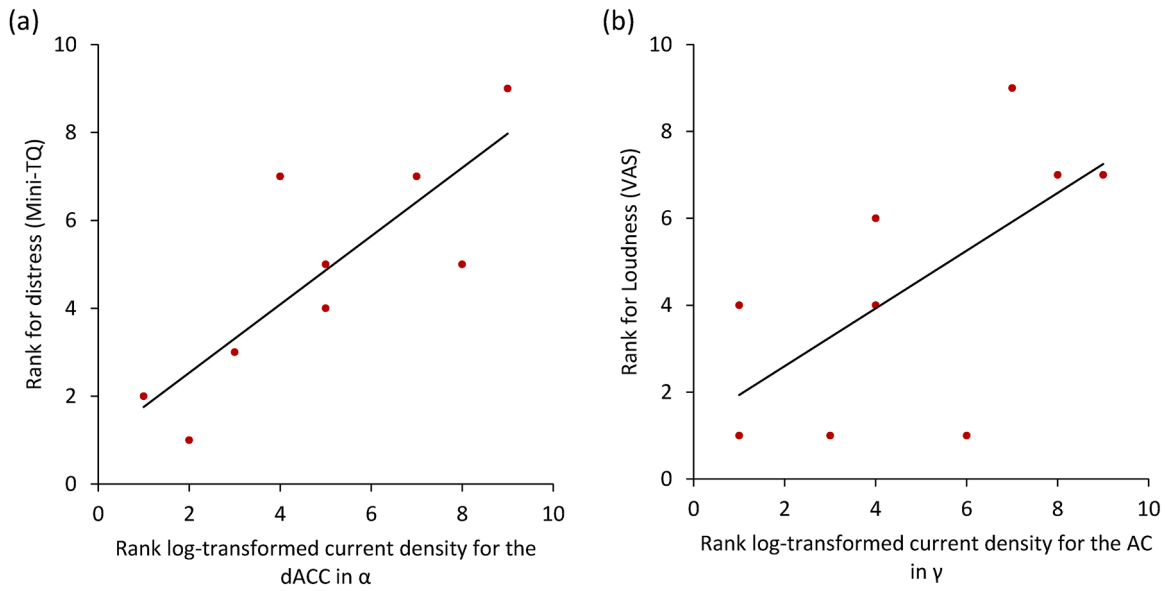

Fig. 5. (a) A spearman correlation between log-transformed current density for the dorsal anterior cingulate cortex (dACC) at the alpha frequency band and distress revealed a significant positive association. (b) A spearman correlation between log-transformed current density for the auditory cortex (AC) at the gamma frequency band and loudness revealed a significant positive association.

When comparing tinnitus participants not perceiving tinnitus and control subjects, a significantly increased functional connectivity was obtained for the alpha frequency band between the pregenual anterior cingulate cortex and auditory cortex during perceiving tinnitus (F = 4.76, p < .05). No effect was obtained between the dorsal anterior cingulate cortex and both the auditory cortex and the pregenual anterior cingulate cortex. No significant effects were obtained when comparing tinnitus and non-tinnitus subjects for the delta, theta, beta and gamma frequency bands. See bottom Fig. 6.

3.7. Cross-frequency effective connectivity

Our results revealed a significant increase for communication going from rostral to dorsal anterior cingulate cortex in alpha, to the pregenual anterior cingulate cortex in theta during tinnitus perception (M = 0.024, Sd = 0.020) in comparison to not perceiving tinnitus (M = 0.008, Sd = 0.009; W = 2.67; p = .008) or controls (M = 0.008, Sd = 0.009; U = 2.08; p = .040). A comparison between not perceiving tinnitus and control subjects revealed no significant effect (U = 0.22 p = .86) (see Fig. 7).

No significant effect was obtained for communication going from the pregenual anterior cingulate cortex in theta to the dorsal anterior cingulate cortex in alpha when comparing people perceiving tinnitus and not perceiving tinnitus (W = 0.89; p = .37). Also, no significant effect was obtained when comparing participants during tinnitus perception and control subjects (U = 1.54; p = .14) as well as not perceiving tinnitus and control subjects (U = 0.75; p = .49).

3.8. Phase-amplitude coupling

A comparison between tinnitus perception and not perceiving tinnitus or controls for theta-gamma coupling in the auditory cortex revealed a significant increase in theta-gamma coupling during tinnitus perception (M = 1.48, Sd = 0.07) in comparison to not perceiving tinnitus (M = 0.017, Sd = 0.007; W = 2.66; p = .008) or controls (M = 0.011, Sd = 0.006; U = 3.58; p < .001). A comparison between not perceiving tinnitus and control subjects revealed no significant effect (U = 1.54 p = .14). See Fig. 8.

4. Discussion

In the present study, we investigated how the onset of tinnitus is modulated by functional changes in the cerebral cortex using resting state EEG. Resting state EEG is an important technique that provides direct information regarding underlying neuronal activity. The advantage of EEG is that it is collected in quiet environments (unlike functional MRI) and can measure spontaneous brain activity in the resting state. Since our recordings were performed in the absence of any stimulus, we can assume that these areas demonstrate continuously increased and decreased changes in activity and connectivity in tinnitus patients. See Fig. 9 for a summary of our findings.

A group comparison between the tinnitus and no-tinnitus state at sensor level revealed increased theta, alpha and gamma power in mid-frontal, frontal and temporal areas, respectively. When applying source reconstruction this translates into increased activity for the pregenual anterior cingulate cortex in theta, rostral to dorsal anterior cingulate cortex in alpha, and auditory cortex, lateral anterior mid-temporal and lateral inferior parietal areas in gamma. The tinnitus on-state differs from healthy controls by theta and gamma power in mid-frontal, and temporal areas, respectively. Source reconstruction revealed increased activity in the pregenual anterior cingulate cortex and gamma in the lateral anterior mid-temporal and ventrolateral prefrontal cortex. The tinnitus-free state differs from healthy controls by alpha in mid-frontal areas, that translate in the pregenual anterior cingulate cortex using source reconstruction. A region of interest analysis further demonstrates that the pregenual anterior cingulate cortex in the no-tinnitus state differs in alpha also from both the tinnitus state (and healthy controls). Tinnitus differs from no-tinnitus and healthy controls in theta in the pregenual anterior cingulate cortex, and in alpha in dorsal anterior cingulate cortex from both no-tinnitus state and healthy controls, as well as gamma in the auditory cortex. Alpha in the dorsal anterior cingulate cortex correlates with tinnitus distress and gamma in auditory cortex with loudness.

The pregenual anterior cingulate cortex is known to be the main hub of a descending inhibitory pathway which normally oscillates at rest in theta (Marinkovic and Rosen, 2022; Rauschecker et al., 2015). Our data reveal that when tinnitus patients do not perceive their tinnitus, increased alpha is present in the pregenual anterior cingulate cortex. This fits with previous findings in hearing loss patients that do not

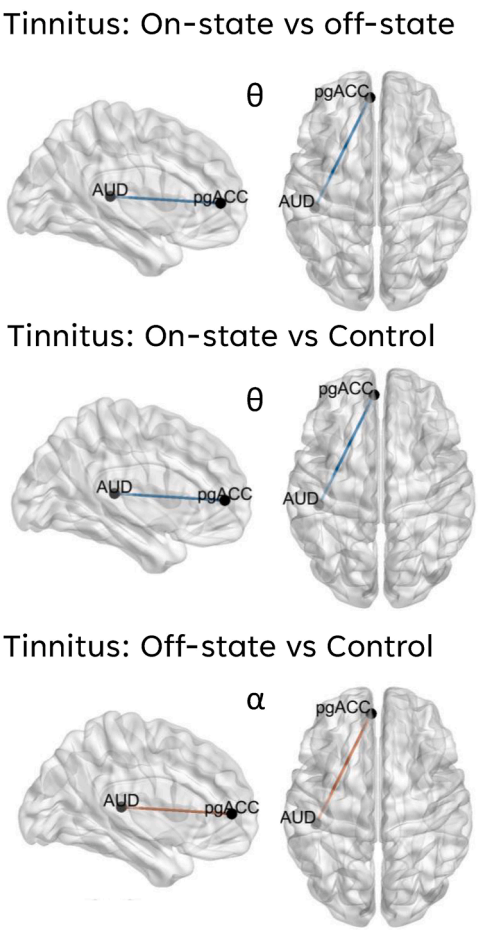

Fig. 6. When comparing participants while perceiving tinnitus and not perceiving tinnitus, a significant reduced connectivity was observed for the theta frequency band between the pregenual anterior cingulate cortex (pgACC) and auditory cortex (AC) during perceiving tinnitus. A similar effect was obtained when we are comparing participants during perceiving tinnitus and control subjects. When we are comparing participants during not perceiving tinnitus and control subjects, a significant increased connectivity was found for the alpha frequency band between the pregenual anterior cingulate cortex and auditory cortex during perceiving tinnitus.

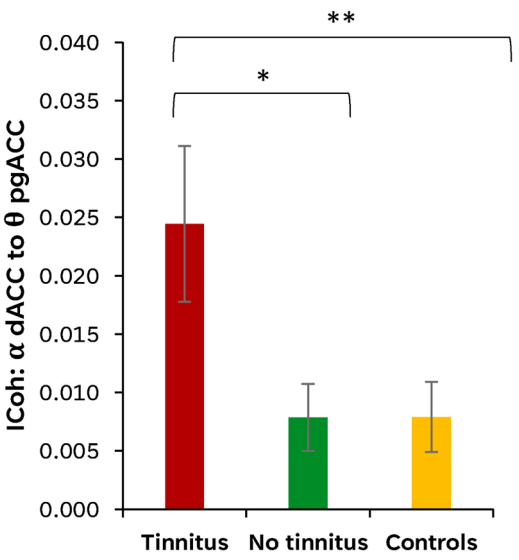

Fig. 7. Our results revealed a significant increase for communication going from dorsal anterior cingulate cortex in alpha to the pregenual anterior cingulate cortex (pgACC) in theta during perceiving tinnitus in comparison to not perceiving tinnitus or controls.

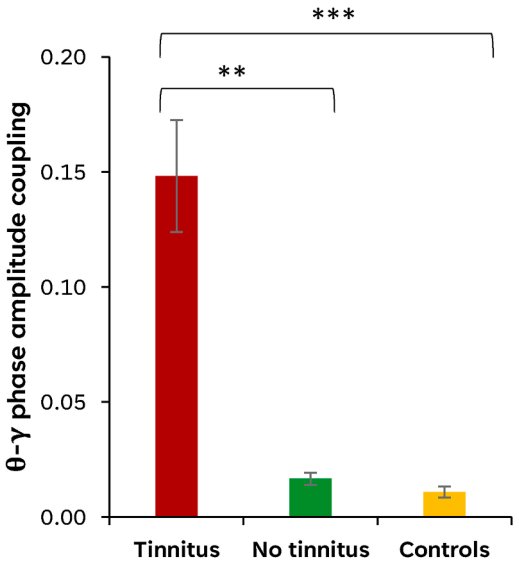

Fig. 8. A comparison between during perceiving tinnitus in comparison to not perceiving tinnitus or controls for theta-gamma coupling in the auditory cortex, revealed a significant increase in theta-gamma coupling during perceiving tinnitus in comparison to not perceiving tinnitus or controls.

perceive tinnitus, where the pregenual anterior cingulate cortex is activated in the alpha frequency band while in patients with no hearing loss with tinnitus the alpha activity is slowed down to theta activity (Vanneste et al., 2019a). Moreover, during the resting state, a functioning top-down noise-cancelling mechanism primarily operates in the alpha frequency band (De Ridder et al., 2015b). However, in cases of dysfunctional noise cancellation, theta activity is expected to dominate (De Ridder et al., 2015b). Initial indications of this were observed in a study investigating selective enriched acoustic stimulation, where overcompensation for hearing loss was employed (Vanneste et al., 2012). The deterioration of patients' clinical conditions correlated with heightened theta activity in the pregenual anterior cingulate cortex, concomitant with increased gamma activity in the auditory cortex (Vanneste et al., 2012). Conversely, the application of bifrontal transcranial direct current stimulation or vagus nerve stimulation has been shown to alleviate tinnitus perception, accompanied by a reduction in theta and gamma band activity in the auditory cortex state (De Ridder et al., 2015b; Langguth et al., 2013; Leaver, 2024; Martins et al., 2022; Vanneste et al., 2017), and an associated increase in alpha activity in the pregenual anterior cingulate cortex (Vanneste and De Ridder, 2011).

When participants report not perceiving the tinnitus percept, activation in both pregenual anterior cingulate cortex and left auditory cortex in the alpha frequency is identified and associated with increased alpha connectivity between these two brain areas. Based on the rhythmic thalamocortical dynamics, normal resting-state activity in the sensory areas, including the auditory cortex, when not perceiving anything is in alpha (Lorenz et al., 2009; van der Loo et al., 2009; Weisz et al., 2007, 2005). Furthermore, this fits with recent findings in chronic pain which demonstrated that during pain suppression the pregenual anterior cingulate cortex accelerates from theta to alpha (Vanneste and De Ridder, 2023).

A secondary exploratory analysis revealed further functional connectivity in theta between pregenual anterior cingulate cortex and auditory cortex is decreased in tinnitus versus no-tinnitus and healthy controls, but is increased in alpha in the no-tinnitus state versus healthy controls. Effective connectivity differs between tinnitus on and off-state

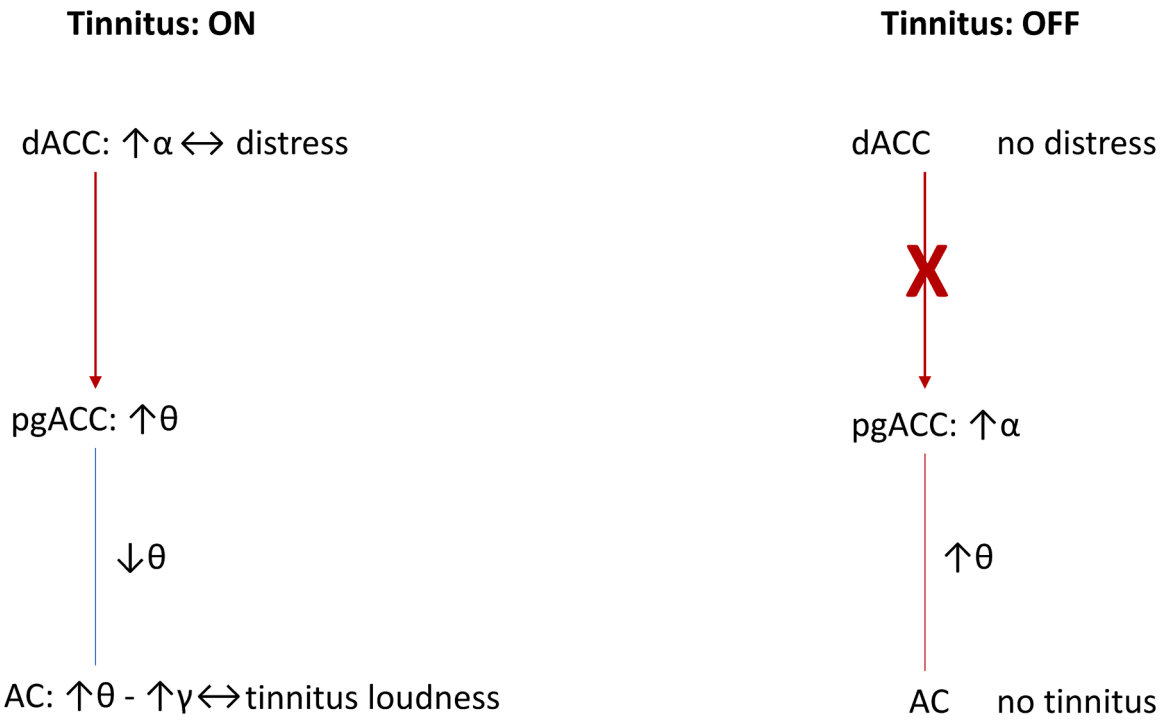

Fig. 9. Summary figure. dorsal anterior cingulate cortex (dACC); pregenual anterior cingulate cortex (pgACC); auditory cortex (AC). Blue lines indicates reduced connectivity; Red lines indicate increase connectivity.

and healthy controls by increased effective connectivity between dorsal anterior cingulate cortex and pregenual anterior cingulate cortex. Theta-gamma cross-frequency coupling is increased in the tinnitus versus no-tinnitus state and healthy controls. It is imperative to underscore that these latter findings are solely exploratory and necessitate further validation through additional research.

Our results suggest that distress is reflected by increased activity in the rostral to dorsal anterior cingulate cortex. This is in agreement with previous tinnitus research that identifies the subgenual and dorsal anterior cingulate cortex as playing a role in tinnitus-related distress (Vanneste et al., 2014, 2010a). It may be that distress, reflected by alpha activity in the rostral to dorsal anterior cingulate cortex, can modulate the onset of tinnitus via theta activity in the pregenual anterior cingulate cortex, however since our data does not capture the moment of tinnitus onset, we cannot directly validate this interpretation. Our results support the association between distress and tinnitus perception, particularly in the on-state, and future research should consider the possibility that distress may itself act as a trigger of the on-switch for tinnitus perception. Increased activity in the dorsal anterior cingulate cortex in the alpha frequency band, slows down activity from alpha to theta in the pregenual anterior cingulate cortex. This suggests that the dorsal anterior cingulate cortex is inhibiting activity in the pregenual anterior cingulate cortex. This is similar to what has been observed in chronic neuropathic pain (De Ridder et al., 2021a; Vanneste and De Ridder, 2023). It is also in keeping with fMRI studies demonstrating that bold activity in the pregenual anterior cingulate extending into the ventromedial prefrontal cortex is modulated when activity in the dorsal anterior cingulate cortex declines (Heilbronner and Hayden, 2016). As mentioned, stress-induced volumetric reduction of the pregenual anterior cingulate cortex is reversible (Soares et al., 2012). This is in accordance with previous research in rodents and primates showing that stress-induced changes in the structure of the prefrontal cortex are reversible, and reinforced via synaptic adaptations, at both the structural and physiological levels (Cerqueira et al., 2007). This may parallel with our findings demonstrating that when participants perceive no tinnitus, activity from pregenual anterior cingulate returns back from theta to alpha.

Secondly, when a tinnitus subject perceives tinnitus, the pregenual anterior cingulate cortex slows down from alpha to theta, and this is associated with a decrease in functional connectivity between the pregenual anterior cingulate cortex and the left auditory cortex, resulting in an increase in auditory cortex gamma band activity. These findings fit with the thalamocortical dysrhythmia model that proposes that normal resting-state alpha activity slows down to theta frequencies in states of deprived input, potentially in the thalamic reticular nucleus because of deficient top-down inhibitory pathways (De Ridder et al., 2015b; Llinas et al., 2005, 1999; Vanneste et al., 2018). This theta activity in the auditory cortex is then coupled to an increase in surrounding gamma activity. Changes of input because of deficient top-down inhibitory pathways can result in a reduction of $GABA_A$-mediated lateral inhibition, inducing gamma band activity surrounding the deafferented thalamocortical columns (Llinas et al., 2005). In addition, we found phase–amplitude coupling between the theta and gamma frequency bands at the auditory cortex in tinnitus participants when they perceive tinnitus. Cross-frequency coupling might be important for integration via low-frequency theta coherence of distributed, geographically focal, high-frequency activity (Lisman and Jensen, 2013).

Furthermore, we obtained increased activity in the inferior parietal lobule during the perception of the tinnitus in comparison to not perceiving the tinnitus percept. These functional changes might indicate the participation of the attention system in tinnitus (De Ridder et al., 2014). This corroborates recent findings combining near-infrared spectroscopy and EEG showing that the inferior parietal cortex contributes to attentional regulation in tinnitus patients (Wertz et al., 2023). The parietal cortex is viewed as a central control node for attention (Behrmann et al., 2004), likely functioning to direct attention and convert accompanying sensory processes into a phantom percept. This is supported by a computer-based model (Sedley, 2019). Another possibility is that the inferior parietal lobule sends information to the default mode network, supported by activity in the lateral anterior mid temporal cortex, which is also a component of the self-referential default mode network. It has been proposed that in chronic tinnitus the tinnitus becomes embodied, i.

e. part of the self-percept, part of who you are (De Ridder et al., 2022; Lee et al., 2021), analogous to what has been proposed in chronic pain (De Ridder et al., 2021a). This may have an energy saving effect (Song et al., 2021). The lateral anterior mid temporal cortex has been shown, using a different kind of EEG processing, namely microstate analysis, to be involved in both chronic pain and tinnitus (De Ridder et al., 2023; Vanneste et al., 2019b).

Although numerous open questions still need to be addressed, the integration of these findings might give a new impetus to the prevention and treatment of tinnitus. As prevention significantly depends on an individual's predisposition, a standardized assessment of the individual susceptibility and resilience to chronic stress might be desirable in tinnitus patients. With improved understanding of the chronification of tinnitus, adapted treatment strategies form those which already exist such as cognitive-behavioral therapy and physiotherapy, as well as pharmacotherapy to modulate the stress at an early stage, could improve outcomes for tinnitus patients who otherwise develop chronic tinnitus. Our findings also open avenues for novel treatment approaches for tinnitus. Novel pharmacological interventions and neuromodulation strategies targeting the dorsal and/or pregenual anterior cingulate regions may hold promise. Moreover, the connection we have supported between stress and tinnitus, along with the recognition of stress as a known modifier of epigenetic markers (Franklin et al., 2012), suggests that tinnitus could, in part, result from epigenetic alterations. Numerous studies have linked such epigenetic modifications to experimentally induced behavioral changes akin to those reported in patients dealing with depression or anxiety (Bagot et al., 2014). Additionally, research indicates that the pattern of epigenetic changes differs between healthy individuals and those with hearing impairments (Provenzano and Domann, 2007). Given that tinnitus sufferers often experience hearing loss and report distress, it is reasonable to assume that certain epigenetic targets may also prove significant in understanding and addressing this condition.

Overall, this unique dataset provides us with the opportunity to gain a better understanding for the potential role distress plays in tinnitus. Although the lower sample size, it needs to be emphasized that is a unique cohort as, for most chronic tinnitus patients, the phantom sound is always present. It is here we stress the necessity for replication, as indeed the unique cohort limits sample sizes, and thus further replication from multiple centers would help to solidify the findings here and improve generalizability. We also acknowledge that while our sample size is below common EEG sample sizes, our sample is still consistent with other EEG studies which investigate disorders with low prevalence. Indeed small EEG studies have been successful in classifying electrophysiological characteristics, with which we believe our study is compatible given its relatively small sample size (Koops et al., 2019). We also recognize that while tinnitus patients received EEG recordings twice, controls received only one EEG recording. However, we do not believe this repeated scanning is inducing any repetition effects, considering that retest reliability for eyes-closed rsEEG is considerably high (Corsi-Cabrera et al., 2007). Furthermore, longitudinal research could further explore the situation just before the onset of tinnitus. That is, whether specific physical and/or mental stressors initiated the onset. One drawback of this study lies in its limited spatial resolution for source localization due to the small number of sensors (19 electrodes) and the absence of subject-specific anatomical forward models. While sufficient for source reconstruction, this setup leads to increased uncertainty in source localization and reduced anatomical precision. Consequently, the spatial accuracy of this study is notably inferior to that of functional MRI. Nonetheless, the tomography sLORETA method has undergone significant validation through studies combining it with other established localization techniques such as functional Magnetic Resonance Imaging (fMRI) (Mulert et al., 2004; Vitacco et al., 2002), structural MRI (Worrell et al., 2000), and Positron Emission Tomography (PET) (Dierks et al., 2000; Pizzagalli et al., 2004; Zumsteg et al., 2005). It has also been utilized in previous research to detect activity in regions like the auditory cortex, the pregenual and dorsal anterior cingulate cortex (Vanneste et al., 2019a, 2010b, 2011b; Zaehle et al., 2007). Further validation of sLORETA has been achieved by comparing its localization findings with those obtained from invasive implanted depth electrodes, as seen in epilepsy studies (Zumsteg et al., 2006a, 2006c) and cognitive ERPs (Volpe et al., 2007). Notably, structures like the anterior cingulate cortex (Pizzagalli et al., 2001) and mesial temporal cortex (Zumsteg et al., 2006b) can be accurately localized using these methods. The involvement of the parahippocampus was previously indicated in research using low-density EEG and later confirmed by PET and MRI, endorsing the reliability of our findings.

5. Conclusion

The EEG data show that tinnitus is triggered by increased theta activity in the pregenual anterior cingulate cortex, associated with decreased theta functional connectivity between the pregenual anterior cingulate cortex and the auditory cortex, as well as increased alpha effective connectivity from the dorsal anterior cingulate cortex to theta in the pregenual anterior cingulate cortex. The no-tinnitus state is not the same as healthy subjects, as alpha in the pregenual anterior cingulate cortex as well as increased alpha functional connectivity between the pregenual anterior cingulate cortex and auditory cortex differentiates the two. This suggests that the tinnitus on-off switch involves increased theta in the pregenual anterior cingulate cortex, but is associated with decreased theta functional connectivity between pregenual anterior cingulate cortex and the auditory cortex, resulting in increased theta-gamma cross-frequency coupling, linked to loudness perception. This most likely represents a deficient noise-canceling mechanism. This occurs under the influence of the dorsal anterior cingulate cortex, part of the salience network (in alpha), likely inhibiting the pregenual anterior cingulate cortex. Moreover, the alpha in the dorsal anterior cingulate cortex correlates with distress. This suggests that when the tinnitus is deemed salient, increased distress inhibits the noise canceling mechanism. When the pregenual anterior cingulate cortex increases its activity to alpha it is capable of transiently suppressing the phantom sound by increased theta functional connectivity to the auditory cortex, likely by activating the noise canceling system. Furthermore, in view of the analogy of the underlying pathophysiology of tinnitus, pain, Parkinson`s disease (Vanneste et al., 2018) and slow wave epilepsy (Llinas et al., 1999), there is no reason to believe this concept could not be extended to other subjective states.

CRediT authorship contribution statement

Sven Vanneste: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Gabriel Byczynski:** Writing – review & editing. **Thierry Verplancke:** Writing – original draft. **Jan Ost:** Data curation. **Jae-Jin Song:** Writing – review & editing, Writing – original draft. **Dirk De Ridder:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors have no conflicts of interest to disclose concerning the research paper.

Data availability

Data and coding is available on request in agreement with ethics approval.

References

Axelsson, A., Ringdahl, A., 1989. Tinnitus–a study of its prevalence and characteristics. Br. J. Audiol. 23 (1), 53–62.

Baccala, L.A., Sameshima, K., 2001. Partial directed coherence: a new concept in neural structure determination. Biol. Cybern. 84 (6), 463–474. https://doi.org/10.1007/PL00007990.

Bagot, R.C., Labonte, B., Pena, C.J., Nestler, E.J., 2014. Epigenetic signaling in psychiatric disorders: stress and depression. Dialogues Clin. Neurosci. 16 (3), 281–295. https://doi.org/10.31887/DCNS.2014.16.3/rbagot.

Barrett, A.B., Murphy, M., Bruno, M.A., Noirhomme, Q., Boly, M., Laureys, S., Seth, A.K., 2012. Granger causality analysis of steady-state electroencephalographic signals during propofol-induced anaesthesia. PLoS ONE 7 (1), e29072. https://doi.org/10.1371/journal.pone.0029072.

Behrmann, M., Geng, J.J., Shomstein, S., 2004. Parietal cortex and attention. Curr. Opin. Neurobiol. 14 (2), 212–217. https://doi.org/10.1016/j.conb.2004.03.012.

Bhatt, J.M., Bhattacharyya, N., Lin, H.W., 2017. Relationships between tinnitus and the prevalence of anxiety and depression. Laryngoscope 127 (2), 466–469. https://doi.org/10.1002/lary.26107.

Biswas, R., Genitsaridi, E., Trpchevska, N., Lugo, A., Schlee, W., Cederroth, C.R., Gallus, S., Hall, D.A., 2023. Low evidence for tinnitus risk factors: a systematic review and meta-analysis. J. Assoc. Res. Otolaryngol. 24 (1), 81–94. https://doi.org/10.1007/s10162-022-00874-y.

Biswas, R., Lugo, A., Akeroyd, M.A., Schlee, W., Gallus, S., Hall, D.A., 2022. Tinnitus prevalence in Europe: a multi-country cross-sectional population study. Lancet Reg. Health Eur. 12, 100250 https://doi.org/10.1016/j.lanepe.2021.100250.

Bloomfield, P., 2000. Fourier analysis of time series: an introduction, second edition. John Wiley & Sons, Inc, New York, p. 261.

Bosman, C.A., Schoffelen, J.M., Brunet, N., Oostenveld, R., Bastos, A.M., Womelsdorf, T., Rubehn, B., Stieglitz, T., De Weerd, P., Fries, P., 2012. Attentional stimulus selection through selective synchronization between monkey visual areas. Neuron 75 (5), 875–888. https://doi.org/10.1016/j.neuron.2012.06.037.

British Society of Audiology, 2008. Recommended procedure: pure tone air and bone conduction threshold audiometry with and without masking and determination of uncomfortable loudness levels.

Canolty, R.T., Edwards, E., Dalal, S.S., Soltani, M., Nagarajan, S.S., Kirsch, H.E., Berger, M.S., Barbaro, N.M., Knight, R.T., 2006. High gamma power is phase-locked to theta oscillations in human neocortex. Science 313 (5793), 1626–1628. https://doi.org/10.1126/science.1128115, 313/5793/1626 [pii].

Cerqueira, J.J., Mailliet, F., Almeida, O.F., Jay, T.M., Sousa, N., 2007. The prefrontal cortex as a key target of the maladaptive response to stress. J. Neurosci. 27 (11), 2781–2787. https://doi.org/10.1523/JNEUROSCI.4372-06.2007.

Congedo, M., 2002. EureKa! (Version 3.0) [Computer Software]. NovaTech EEG Inc, Knoxville, TN. Freeware available at. www.NovaTechEEG.

Congedo, M., John, R.E., De Ridder, D., Prichep, L., Isenhart, R., 2010. On the "dependence" of "independent" group EEG sources; an EEG study on two large databases. Brain Topogr. 23 (2), 134–138. https://doi.org/10.1007/s10548-009-0113-6.

Corsi-Cabrera, M., Galindo-Vilchis, L., del-Rio-Portilla, Y., Arce, C., Ramos-Loyo, J., 2007. Within-subject reliability and inter-session stability of EEG power and coherent activity in women evaluated monthly over nine months. Clin. Neurophysiol. 118 (1), 9–21. https://doi.org/10.1016/j.clinph.2006.08.013.

De Ridder, D., Adhia, D., Vanneste, S., 2021a. The anatomy of pain and suffering in the brain and its clinical implications. Neurosci. Biobehav. Rev. 130, 125–146. https://doi.org/10.1016/j.neubiorev.2021.08.013.

De Ridder, D., Congedo, M., Vanneste, S., 2015a. The neural correlates of subjectively perceived and passively matched loudness perception in auditory phantom perception. Brain Behav. e00331. https://doi.org/10.1002/brb3.331.

De Ridder, D., Friston, K., Sedley, W., Vanneste, S., 2023. A parahippocampal-sensory Bayesian vicious circle generates pain or tinnitus: a source-localized EEG study. Brain Commun. 5 (3), fcad132. https://doi.org/10.1093/braincomms/fcad132.

De Ridder, D., Schlee, W., Vanneste, S., Londero, A., Weisz, N., Kleinjung, T., Shekhawat, G.S., Elgoyhen, A.B., Song, J.J., Andersson, G., Adhia, D., de Azevedo, A. A., Baguley, D.M., Biesinger, E., Binetti, A.C., Del Bo, L., Cederroth, C.R., Cima, R., Eggermont, J.J., Figueiredo, R., Fuller, T.E., Gallus, S., Gilles, A., Hall, D.A., Van de Heyning, P., Hoare, D.J., Khedr, E.M., Kikidis, D., Kleinstaeuber, M., Kreuzer, P.M., Lai, J.T., Lainez, J.M., Landgrebe, M., Li, L.P., Lim, H.H., Liu, T.C., Lopez-Escamez, J. A., Mazurek, B., Moller, A.R., Neff, P., Pantev, C., Park, S.N., Piccirillo, J.F., Poeppl, T.B., Rauschecker, J.P., Salvi, R., Sanchez, T.G., Schecklmann, M., Schiller, A., Searchfield, G.D., Tyler, R., Vielsmeier, V., Vlaeyen, J.W.S., Zhang, J., Zheng, Y., de Nora, M., Langguth, B., 2021b. Tinnitus and tinnitus disorder: theoretical and operational definitions (an international multidisciplinary proposal). Prog. Brain Res. 260, 1–25. https://doi.org/10.1016/bs.pbr.2020.12.002.

De Ridder, D., Vanneste, S., Langguth, B., Llinas, R., 2015b. Thalamocortical dysrhythmia: a theoretical update in tinnitus. Front. Neurol. 6, 124. https://doi.org/10.3389/fneur.2015.00124.

De Ridder, D., Vanneste, S., Smith, M., Adhia, D., 2022. Pain and the triple network model. Front. Neurol. 13, 757241 https://doi.org/10.3389/fneur.2022.757241.

De Ridder, D., Vanneste, S., Weisz, N., Londero, A., Schlee, W., Elgoyhen, A.B., Langguth, B., 2014. An integrative model of auditory phantom perception: tinnitus as a unified percept of interacting separable subnetworks. Neurosci. Biobehav. Rev. 44, 16–32. https://doi.org/10.1016/j.neubiorev.2013.03.021.

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 (10), 1817–1824. S1388245700004272 [pii].

Franklin, T.B., Saab, B.J., Mansuy, I.M., 2012. Neural mechanisms of stress resilience and vulnerability. Neuron 75 (5), 747–761. https://doi.org/10.1016/j.neuron.2012.08.016.

Friston, K., Moran, R., Seth, A.K., 2013. Analysing connectivity with Granger causality and dynamic causal modelling. Curr. Opin. Neurobiol. 23 (2), 172–178. https://doi.org/10.1016/j.conb.2012.11.010.

Fuchs, M., Kastner, J., Wagner, M., Hawes, S., Ebersole, J.S., 2002. A standardized boundary element method volume conductor model. Clin. Neurophysiol. 113 (5), 702–712.

Geweke, J., 1982. Measurement of lineair dependence and feedback between multiple time series. J. Am. Stat. Assoc. 77, 304.

Granger, C.W.J., 1969. Investigating causal relations by econometrics models and crosss-spectral methods. Econometrica 37, 424.

Hasson, D., Theorell, T., Wallen, M.B., Leineweber, C., Canlon, B., 2011. Stress and prevalence of hearing problems in the Swedish working population. BMC Public Health 11, 130. https://doi.org/10.1186/1471-2458-11-130.

Heilbronner, S.R., Hayden, B.Y., 2016. Dorsal anterior cingulate cortex: a bottom-up view. Annu. Rev. Neurosci. 39, 149–170. https://doi.org/10.1146/annurev-neuro-070815-013952.

Hiller, W., Goebel, G., 1992. A psychometric study of complaints in chronic tinnitus. J. Psychosom. Res. 36 (4), 337–348.

Hiller, W., Goebel, G., Rief, W., 1994. Reliability of self-rated tinnitus distress and association with psychological symptom patterns. Br. J. Clin. Psychol. 33 (Pt 2), 231–239.

Jarach, C.M., Lugo, A., Scala, M., van den Brandt, P.A., Cederroth, C.R., Odone, A., Garavello, W., Schlee, W., Langguth, B., Gallus, S., 2022. Global prevalence and incidence of tinnitus: a systematic review and meta-analysis. JAMA Neurol. 79 (9), 888–900. https://doi.org/10.1001/jamaneurol.2022.2189.

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 (4), 1600–1611.

Koops, E.A., Husain, F.T., van Dijk, P., 2019. Profiling intermittent tinnitus: a retrospective review. Int. J. Audiol. 58 (7), 434–440. https://doi.org/10.1080/14992027.2019.1600058.

Lancaster, J.L., Woldorff, M.G., Parsons, L.M., Liotti, M., Freitas, C.S., Rainey, L., Kochunov, P.V., Nickerson, D., Mikiten, S.A., Fox, P.T., 2000. Automated Talairach atlas labels for functional brain mapping. Hum. Brain Mapp. 10 (3), 120–131.

Langguth, B., Kreuzer, P.M., Kleinjung, T., De Ridder, D., 2013. Tinnitus: causes and clinical management. Lancet Neurol. 12 (9), 920–930. https://doi.org/10.1016/S1474-4422(13)70160-1.

Leaver, A.M., 2024. Perceptual and cognitive effects of focal tDCS of auditory cortex in tinnitus. medRxiv. https://doi.org/10.1101/2024.01.31.24302093.

Leaver, A.M., Renier, L., Chevillet, M.A., Morgan, S., Kim, H.J., Rauschecker, J.P., 2011. Dysregulation of limbic and auditory networks in tinnitus. Neuron 69 (1), 33–43. https://doi.org/10.1016/j.neuron.2010.12.002.

Lee, S.Y., Chang, M., Kwon, B., Choi, B.Y., Koo, J.W., Moon, T., De Ridder, D., Vanneste, S., Song, J.J., 2021. Is the posterior cingulate cortex an on-off switch for tinnitus?: a comparison between hearing loss subjects with and without tinnitus. Hear. Res. 411, 108356 https://doi.org/10.1016/j.heares.2021.108356.

Lisman, J.E., Jensen, O., 2013. The theta-gamma neural code. Neuron 77 (6), 1002–1016. https://doi.org/10.1016/j.neuron.2013.03.007.

Llinas, R., Urbano, F.J., Leznik, E., Ramirez, R.R., van Marle, H.J., 2005. Rhythmic and dysrhythmic thalamocortical dynamics: GABA systems and the edge effect. Trends Neurosci. 28 (6), 325–333. https://doi.org/10.1016/j.tins.2005.04.006.

Llinas, R.R., Ribary, U., Jeanmonod, D., Kronberg, E., Mitra, P.P., 1999. Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. Proc. Natl. Acad. Sci. USA 96 (26), 15222–15227. https://doi.org/10.1073/pnas.96.26.15222.

Logan, J.M., Sanders, A.L., Snyder, A.Z., Morris, J.C., Buckner, R.L., 2002. Under-recruitment and nonselective recruitment: dissociable neural mechanisms associated with aging. Neuron 33 (5), 827–840.

Lorenz, I., Muller, N., Schlee, W., Hartmann, T., Weisz, N., 2009. Loss of alpha power is related to increased gamma synchronization-a marker of reduced inhibition in tinnitus? Neurosci. Lett. 453 (3), 225–228. https://doi.org/10.1016/j.neulet.2009.02.028. S0304-3940(09)00212-2 [pii].

Lucassen, P.J., Pruessner, J., Sousa, N., Almeida, O.F., Van Dam, A.M., Rajkowska, G., Swaab, D.F., Czeh, B., 2014. Neuropathology of stress. Acta Neuropathol. 127 (1), 109–135. https://doi.org/10.1007/s00401-013-1223-5.

Ma, L., Zhang, J., Yang, P., Wang, E., Qin, L., 2015. Acute restraint stress alters sound-evoked neural responses in the rat auditory cortex. Neuroscience 290, 608–620. https://doi.org/10.1016/j.neuroscience.2015.01.074.

Marinkovic, K., Rosen, B.Q., 2022. Theta oscillatory dynamics of inhibitory control, error processing, and post-error adjustments: neural underpinnings and alcohol-induced dysregulation in social drinkers. Alcohol Clin. Exp. Res. 46 (7), 1220–1232. https://doi.org/10.1111/acer.14856.

Martins, M.L., Souza, D.D.S., Cavalcante, M., Barboza, H.N., de Medeiros, J.F., Dos Santos Andrade, S.M.M., Machado, D., da Rosa, M.R.D., 2022. Effect of transcranial Direct Current Stimulation for tinnitus treatment: a systematic review and meta-analysis. Neurophysiol. Clin. 52 (1), 1–16. https://doi.org/10.1016/j.neucli.2021.12.005.

Mazurek, B., Bocking, B., Dobel, C., Rose, M., Bruggemann, P., 2023. Tinnitus and influencing comorbidities. Laryngorhinootologie 102 (S 01), S50–S58. https://doi.org/10.1055/a-1950-6149.

Mazurek, B., Szczepek, A.J., Hebert, S., 2015. Stress and tinnitus. HNO 63 (4), 258–265. https://doi.org/10.1007/s00106-014-2973-7.
McCombe, A., Baguley, D., Coles, R., McKenna, L., McKinney, C., Windle-Taylor, P., 2001. Guidelines for the grading of tinnitus severity: the results of a working group commissioned by the British Association of Otolaryngologists, Head and Neck Surgeons, 1999. Clin. Otolaryngol. Allied Sci. 26 (5), 388–393, 490 [pii].
McEwen, B.S., Nasca, C., Gray, J.D., 2016. Stress effects on neuronal structure: hippocampus, amygdala, and prefrontal cortex. Neuropsychopharmacology 41 (1), 3–23. https://doi.org/10.1038/npp.2015.171.
Meeus, O., Blaivie, C., Van de Heyning, P., 2007. Validation of the Dutch and the French version of the tinnitus questionnaire. B-ENT 3 (Suppl 7), 11–17.
Misquitta, K.A., Miles, A., Prevot, T.D., Knoch, J.K., Fee, C., Newton, D.F., Ellegood, J., Lerch, J.P., Sibille, E., Nikolova, Y.S., Banasr, M., 2021. Reduced anterior cingulate cortex volume induced by chronic stress correlates with increased behavioral emotionality and decreased synaptic puncta density. Neuropharmacology 190, 108562. https://doi.org/10.1016/j.neuropharm.2021.108562.
Moazami-Goudarzi, M., Michels, L., Weisz, N., Jeanmonod, D., 2010. Temporo-insular enhancement of EEG low and high frequencies in patients with chronic tinnitus. QEEG study of chronic tinnitus patients. BMC Neurosci. 11, 40. https://doi.org/10.1186/1471-2202-11-40, 1471-2202-11-40 [pii].
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 (1), 83–94. https://doi.org/10.1016/j.neuroimage.2003.10.051. S1053811904000084 [pii].
Nichols, T.E., Holmes, A.P., 2002. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum. Brain Mapp. 15 (1), 1–25. https://doi.org/10.1002/hbm.1058 [pii].
Pascual-Marqui, R., 2007. Instantaneous and lagged measurements of linear and nonlinear dependence between groups of multivariate time series: frequency decomposition.
Pascual-Marqui, R., 2007. Discrete, 3D distributed, linear imaging methods of electric neuronal activity. Part 1: exact, zero error localization. http://arxiv.org/abs/0710.3341.
Pascual-Marqui, R.D., 2002. Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. Methods Find. Exp. Clin. Pharmacol. 24 (Suppl D), 5–12.
Pascual-Marqui, R.D., Biscay, R.J., Bosch-Bayard, J., Lehmann, D., Kochi, K., Kinoshita, T., Yamada, N., Sadato, N., 2014a. Assessing direct paths of intracortical causal information flow of oscillatory activity with the isolated effective coherence (iCoh). Front. Hum. Neurosci. 8, 448. https://doi.org/10.3389/fnhum.2014.00448.
Pascual-Marqui, R.D., Biscay, R.J., Bosch-Bayard, J., Lehmann, D., Kochi, K., Yamada, N., Kinoshita, T., Sadato, N., 2014. Isolated effective coherence (iCoh): causal information flow excluding indirect paths. arxiv, https://arxiv.org/ftp/arxiv/papers/1402/1402.4887.pdf.
Pascual-Marqui, R.D., Lehmann, D., Koukkou, M., Kochi, K., Anderer, P., Saletu, B., Tanaka, H., Hirata, K., John, E.R., Prichep, L., Biscay-Lirio, R., Kinoshita, T., 2011. Assessing interactions in the brain with exact low-resolution electromagnetic tomography. Philos. Trans. A Math. Phys. Eng. Sci. 369 (1952), 3768–3784. https://doi.org/10.1098/rsta.2011.0081.
Pearl, J., 2000. Causality. Cambridge University Press., New York.
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. Am. J. Psychiatry 158 (3), 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 (4), 393–405. https://doi.org/10.1038/sj.mp.4001469, 3254001469 [pii].
Probst, T., Pryss, R., Langguth, B., Schlee, W., 2016. Emotional states as mediators between tinnitus loudness and tinnitus distress in daily life: results from the "TrackYourTinnitus" application. Sci. Rep. 6, 20382. https://doi.org/10.1038/srep20382.
Provenzano, M.J., Domann, F.E., 2007. A role for epigenetics in hearing: establishment and maintenance of auditory specific gene expression patterns. Hear. Res. 233 (1–2), 1–13. https://doi.org/10.1016/j.heares.2007.07.002.
Rauschecker, J.P., leaver, A.M., Muhlau, M., 2010. Tuning out the noise: limbic-auditory interactions in tinnitus. Neuron 66 (6), 819–826.
Rauschecker, J.P., May, E.S., Maudoux, A., Ploner, M., 2015. Frontostriatal gating of tinnitus and chronic pain. Trends Cogn. Sci. 19 (10), 567–578. https://doi.org/10.1016/j.tics.2015.08.002.
Schelter, B., Timmer, J., Eichler, M., 2009. Assessing the strength of directed influences among neural signals using renormalized partial directed coherence. J. Neurosci. Methods 179 (1), 121–130. https://doi.org/10.1016/j.jneumeth.2009.01.006.
Sedley, W., 2019. Tinnitus: does gain explain? Neuroscience 407, 213–228. https://doi.org/10.1016/j.neuroscience.2019.01.027.
Siepmann, M., Kirch, W., 2002. Effects of caffeine on topographic quantitative EEG. Neuropsychobiology 45 (3), 161–166.
Soares, J.M., Sampaio, A., Ferreira, L.M., Santos, N.C., Marques, F., Palha, J.A., Cerqueira, J.J., Sousa, N., 2012. Stress-induced changes in human decision-making are reversible. Transl. Psychiatry 2, e131. https://doi.org/10.1038/tp.2012.59.
Song, J.J., Park, J., Koo, J.W., Lee, S.Y., Vanneste, S., De Ridder, D., Hong, S., Lim, S., 2021. The balance between Bayesian inference and default mode determines the generation of tinnitus from decreased auditory input: a volume entropy-based study. Hum. Brain Mapp. 42 (12), 4059–4073. https://doi.org/10.1002/hbm.25539.
Song, J.J., Vanneste, S., De Ridder, D., 2015. Dysfunctional noise cancelling of the rostral anterior cingulate cortex in tinnitus patients. PLoS ONE 10 (4), e0123538. https://doi.org/10.1371/journal.pone.0123538.
Stokes, P.A., Purdon, P.L., 2017. A study of problems encountered in Granger causality analysis from a neuroscience perspective. Proc. Natl. Acad. Sci. USA 114 (34), E7063–E7072. https://doi.org/10.1073/pnas.1704663114.
van der Loo, E., Gais, S., Congedo, M., Vanneste, S., Plazier, M., Menovsky, T., Van de Heyning, P., De Ridder, D., 2009. Tinnitus intensity dependent gamma oscillations of the contralateral auditory cortex. PLoS ONE 4 (10), e7396. https://doi.org/10.1371/journal.pone.0007396.
Vanneste, S., Alsalman, O., De Ridder, D., 2019a. Top-down and bottom-up regulated auditory phantom perception. J. Neurosci. 39 (2), 364–378. https://doi.org/10.1523/JNEUROSCI.0966-18.2018.
Vanneste, S., Congedo, M., De Ridder, D., 2014. Pinpointing a highly specific pathological functional connection that turns phantom sound into distress. Cereb. Cortex 24 (9), 2268–2282. https://doi.org/10.1093/cercor/bht068.
Vanneste, S., De Ridder, D., 2011. Bifrontal transcranial direct current stimulation modulates tinnitus intensity and tinnitus-distress-related brain activity. Eur. J. Neurosci. 34 (4), 605–614. https://doi.org/10.1111/j.1460-9568.2011.07778.x.
Vanneste, S., De Ridder, D., 2023. BurstDR spinal cord stimulation rebalances pain input and pain suppression in the brain in chronic neuropathic pain. Brain Stimul. 16 (4), 1186–1195. https://doi.org/10.1016/j.brs.2023.07.058.
Vanneste, S., Martin, J., Rennaker 2nd, R.L., Kilgard, M.P., 2017. Pairing sound with vagus nerve stimulation modulates cortical synchrony and phase coherence in tinnitus: an exploratory retrospective study. Sci. Rep. 7 (1), 17345. https://doi.org/10.1038/s41598-017-17750-y.
Vanneste, S., Plazier, M., der Loo, E., de Heyning, P.V., Congedo, M., De Ridder, D., 2010a. The neural correlates of tinnitus-related distress. Neuroimage 52 (2), 470–480. https://doi.org/10.1016/j.neuroimage.2010.04.029.
Vanneste, S., Plazier, M., van der Loo, E., Ost, J., Meeus, O., Van de Heyning, P., De Ridder, D., 2011a. Validation of the Mini-TQ in a Dutch-speaking population: a rapid assessment for tinnitus-related distress. B-ENT 7 (1), 31–36.
Vanneste, S., Plazier, M., van der Loo, E., Van de Heyning, P., De Ridder, D., 2010b. The difference between uni- and bilateral auditory phantom percept. Clin. Neurophysiol. https://doi.org/10.1016/j.clinph.2010.07.022. S1388-2457(10)00605-X [pii].
Vanneste, S., Plazier, M., van der Loo, E., Van de Heyning, P., De Ridder, D., 2011b. The difference between uni- and bilateral auditory phantom percept. Clin. Neurophysiol. 122 (3), 578–587. https://doi.org/10.1016/j.clinph.2010.07.022 official journal of the International Federation of Clinical Neurophysiology.
Vanneste, S., Song, J.J., De Ridder, D., 2018. Thalamocortical dysrhythmia detected by machine learning. Nat. Commun. 9 (1), 1103. https://doi.org/10.1038/s41467-018-02820-0.
Vanneste, S., To, W.T., De Ridder, D., 2019b. Tinnitus and neuropathic pain share a common neural substrate in the form of specific brain connectivity and microstate profiles. Prog. Neuropsychopharmacol. Biol. Psychiatry 88, 388–400. https://doi.org/10.1016/j.pnpbp.2018.08.015.
Vanneste, S., van Dongen, M., De Vree, B., Hiseni, S., van der Velden, E., Strydis, C., Joos, K., Norena, A., Serdijn, W., De Ridder, D., 2012. Does enriched acoustic environment in humans abolish chronic tinnitus clinically and electrophysiologically? A double blind placebo controlled study. Hear. Res. 296, 141–148. https://doi.org/10.1016/j.heares.2012.10.003. S0378-5955(12)00244-4 [pii].
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 (1), 4–12. https://doi.org/10.1002/hbm.10038.
Volkow, N.D., Logan, J., Fowler, J.S., Wang, G.J., Gur, R.C., Wong, C., Felder, C., Gatley, S.J., Ding, Y.S., Hitzemann, R., Pappas, N., 2000. Association between age-related decline in brain dopamine activity and impairment in frontal and cingulate metabolism. Am. J. Psychiatry 157 (1), 75–80.
Volpe, U., Mucci, A., Bucci, P., Merlotti, E., Galderisi, S., Maj, M., 2007. The cortical generators of P3a and P3b: a LORETA study. Brain Res. Bull. 73 (4–6), 220–230. https://doi.org/10.1016/j.brainresbull.2007.03.003. S0361-9230(07)00097-4 [pii].
Weisz, N., Dohrmann, K., Elbert, T., 2007. The relevance of spontaneous activity for the coding of the tinnitus sensation. Prog. Brain Res. 166, 61–70. https://doi.org/10.1016/S0079-6123(07)66006-3.
Weisz, N., Wienbruch, C., Dohrmann, K., Elbert, T., 2005. Neuromagnetic indicators of auditory cortical reorganization of tinnitus. Brain 128 (Pt 11), 2722–2731. https://doi.org/10.1093/brain/awh588.
Wertz, J., Ruttiger, L., Bender, B., Klose, U., Stark, R.S., Dapper, K., Saemisch, J., Braun, C., Singer, W., Dalhoff, E., Bader, K., Wolpert, S.M., Knipper, M., Munk, M.H. J., 2023. Differential cortical activation patterns: pioneering sub-classification of tinnitus with and without hyperacusis by combining audiometry, gamma oscillations, and hemodynamics. Front. Neurosci. 17, 1232446 https://doi.org/10.3389/fnins.2023.1232446.
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 (4), 273–282.
Yu, X.J., Xu, X.X., He, S., He, J., 2009. Change detection by thalamic reticular neurons. Nat. Neurosci. 12 (9), 1165–1170. https://doi.org/10.1038/nn.2373.
Zaehle, T., Jancke, L., Meyer, M., 2007. Electrical brain imaging evidences left auditory cortex involvement in speech and non-speech discrimination based on temporal features. Behav. Brain Funct. 3, 63. https://doi.org/10.1186/1744-9081-3-63, 1744-9081-3-63 [pii].

Zumsteg, D., Lozano, A.M., Wennberg, R.A., 2006b. Mesial temporal inhibition in a patient with deep brain stimulation of the anterior thalamus for epilepsy. Epilepsia 47 (11), 1958–1962. https://doi.org/10.1111/j.1528-1167.2006.00824.x. EPI824 [pii].

Zumsteg, D., Lozano, A.M., Wennberg, R.A., 2006a. Depth electrode recorded cerebral responses with deep brain stimulation of the anterior thalamus for epilepsy. Clin. Neurophysiol. 117 (7), 1602–1609. https://doi.org/10.1016/j.clinph.2006.04.008. S1388-2457(06)00165-9 [pii].

Zumsteg, D., Lozano, A.M., Wieser, H.G., Wennberg, R.A., 2006c. Cortical activation with deep brain stimulation of the anterior thalamus for epilepsy. Clin. Neurophysiol. 117 (1), 192–207. https://doi.org/10.1016/j.clinph.2005.09.015. S1388-2457(05)00371-8 [pii].

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 (10), 1657–1660. https://doi.org/10.1212/01.wnl.0000184516.32369.1a, 65/10/1657 [pii].