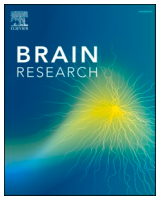
Brain Research 1844 (2024) 149137

Contents lists available at ScienceDirect

Brain Research

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



Research paper

The brain's duck test in phantom percepts: Multisensory congruence in neuropathic pain and tinnitus

Dirk De Ridder [a], Divya Adhia [a], Sven Vanneste [b,c,*]

[a] Unit of Neurosurgery, Department of Surgical Sciences, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand
[b] School of Psychology, Trinity College Dublin, Dublin, Ireland
[c] Global Brain Health Institute & Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland

ARTICLE INFO

Keywords:
Tinnitus
Pain
Parahippocampal
Duck
Multisensory
Cross-modal
Bayes

ABSTRACT

Chronic neuropathic pain and chronic tinnitus have been likened to phantom percepts, in which a complete or partial sensory deafferentation results in a filling in of the missing information derived from memory. 150 participants, 50 with tinnitus, 50 with chronic pain and 50 healthy controls underwent a resting state EEG. Source localized current density is recorded from all the sensory cortices (olfactory, gustatory, somatosensory, auditory, vestibular, visual) as well as the parahippocampal area. Functional connectivity by means of lagged phase synchronization is also computed between these regions of interest. Pain and tinnitus are associated with gamma band activity, reflecting prediction errors, in all sensory cortices except the olfactory and gustatory cortex. Functional connectivity identifies theta frequency connectivity between each of the sensory cortices except the chemical senses to the parahippocampus, but not between the individual sensory cortices. When one sensory domain is deprived, the other senses may provide the parahippocampal 'contextual' area with the most likely sound or somatosensory sensation to fill in the gap, applying an abductive 'duck test' approach, i.e., based on stored multisensory congruence. This novel concept paves the way to develop novel treatments for pain and tinnitus, using multisensory (i.e. visual, vestibular, somatosensory, auditory) modulation with or without associated parahippocampal targeting.

1. Introduction

Chronic neuropathic pain and chronic tinnitus have been likened to phantom percepts, in which a complete or partial sensory deafferentation results in a filling in of the missing information derived from memory (De Ridder et al., 2021a; De Ridder et al., 2014a; De Ridder et al., 2014b; Lee et al., 2017). The Bayesian filling-in of predicted sensory information may reduce the deafferentation-based uncertainty (De Ridder et al., 2014b), following the concept 'better safe than sorry' (Van den Bergh, Brosschot, Critchley, Thayer, & Ottaviani, 2021). In other words, if the sensory deprivation is deemed salient, i.e. behaviorally relevant, the Bayesian brain may reduce the inherent sensory uncertainty by pulling the predicted information from sensory memory (De Ridder & Vanneste, 2021; De Ridder et al., 2014b; Vanneste & De Ridder, 2016). This maladaptive mechanism may then lead to chronic pain or tinnitus (De Ridder et al., 2021b; De Ridder & Vanneste, 2021).

It is hypothesized that this filling in is based on an increase in topographically restricted uncertainty, within one or a few thalamocortical columns within one sensory modality (De Ridder et al., 2014b). For example, a noise trauma would induce deafferentation around 4000 Hz, and the filling in would occur because of a discrepancy of input (i.e. prediction error) between adjacent thalamocortical columns. If 2000 and 6000 Hz thalamocortical columns were still providing normal input to the auditory cortex and 4000 Hz not, then the missing information would be filled in (De Ridder et al., 2014b). This limited the Bayesian filling in to one sensory modality. Yet, sensory systems do not work in isolation: continued exposure to multimodal sensory events sets up expectations about what a given visual object sounds or feels like (Diaconescu, Alain, & McIntosh, 2011). In hierarchical inference the brain uses a kind of abductive reasoning, by means of multisensory integration, to verify whether sensory information is a true reflection of states of affairs in the outside world (Basura, Koehler, & Shore, 2012; Foxe

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

https://doi.org/10.1016/j.brainres.2024.149137
Received 27 February 2024; Received in revised form 26 June 2024; Accepted 1 August 2024
Available online 3 August 2024

et al., 2000; Foxe et al., 2002). Multisensory integration allows for more precise i.e., confident representations than possible with a single sensory system, by accumulating coincident and consistent evidence from each sense (Meredith, 2002; Wu, Stefanescu, Martel, & Shore, 2015). This represents a manifestation of abductive reasoning, colloquially illustrated through the duck test: "*When I see a bird that walks like a duck and swims like a duck and quacks like a duck, I call that bird a duck*" (Riley, 2017). This aligns seamlessly with a Bayesian explanation of perception, where the likelihood of a shared origin rises with consistent multisensory input. This suggests that the process of auditory filling in might not solely rely on retrieving absent details from auditory memory but could also involve contextual, specifically multisensory, memory. Multisensory integration requires multisensory interactions, which means that prediction errors detected in one modality need to be weighted in relation to the precision of sensory input in other senses. For example, I will attend to auditory cues in a dark environment, with imprecise visual cues, but may rely entirely upon my prior memory-based beliefs in the absence of audio-visual sensory information, leading to phantom percepts. But apart from improving the precision of sensory input, multisensory integration may also reduce sensory input that is deemed not salient. For example, somatosensory-auditory interaction may be involved in suppressing self-generated sounds, e.g. in chewing (Shore & Zhou, 2006), and in permitting normal speech (Ohashi & Ito, 2019; Trudeau-Fisette, Ito, & Menard, 2019). Auditory and somatosensory memory is stored in a widely distributed network that incorporates the respective sensory cortex, but also includes the DLPFC, insula, and (para)hippocampus (Alain, Woods, & Knight, 1998; Albanese, Duerden, Rainville, & Duncan, 2007; Bodner, Kroger, & Fuster, 1996; Engelien et al., 2000; Klostermann, Kane, & Shimamura, 2008). Whereas the primary auditory cortex can integrate visual and somatosensory information (Kayser, Petkov, Augath, & Logothetis, 2007), i.e. auditory cortex activity is modulated by visual and somatosensory input (Ahveninen et al., 2024; Morrill & Hasenstaub, 2018), multisensory integration is dependent on the behavioural context (Allman et al., 2008). The parahippocampus, as main hub for context processing, likely embeds the auditory memory in a larger spatial, personal and time context (E. Aminoff, Gronau, & Bar, 2007; E. M. Aminoff, Kveraga, & Bar, 2013; Bar et al., 2008a; Bar et al., 2008b; Baumann & Mattingley, 2016; De Ridder, Friston, Sedley, & Vanneste, 2023; Eichenbaum & Lipton, 2008). As such, the parahippocampal area has been considered a functional interface between perception and memory (Baumann & Mattingley, 2016). Consequently, when a percept is pulled from memory, as is proposed for chronic pain and tinnitus, it is unsurprising that *meta*-analyses have shown that the parahippocampal area is implicated in physical (Smallwood et al., 2013) and psychological (Meerwijk, Ford, & Weiss, 2013) pain as well as tinnitus (Chen et al., 2017; Song et al., 2012a).

A major question is whether cross-modal processing is involved in chronic pain and chronic tinnitus? From a Bayesian brain perspective, is the prediction error, as reflected by gamma band activity (Arnal, Wyart, & Giraud, 2011; Auksztulewicz, Friston, & Nobre, 2017; Cao, Thut, & Gross, 2017; Chao, Takaura, Wang, Fujii, & Dehaene, 2018; Gueguen et al., 2021; Lewis & Bastiaansen, 2015), only computed in the deafferented auditory cortex in tinnitus, or does auditory deafferentation also result in prediction errors in the other sensory cortices, such as the visual, somatosensory, vestibular, gustatory and olfactory cortex due to discrepancies between expected auditory and expected visual, somatosensory, vestibular and other stimuli? Furthermore, how do the different sensory cortices interact in chronic pain and tinnitus? In a previous study we were already able to show that pain and tinnitus are marked by heightened theta activity within the pregenual anterior cingulate cortex, reaching into the lateral prefrontal cortex and medial anterior temporal lobe. Pain and tinnitus were also characterized by increased gamma band activity in both the auditory and somatosensory cortex (De Ridder et al., 2023). These neurophysiological changes extended to the dorsal anterior cingulate cortex and parahippocampus in both pain and tinnitus (De Ridder et al., 2023). A question arises: do the sensory cortices interact directly, or do they communicate indirectly via the contextual multisensory integration mechanism of the parahippocampus? The parahippocampus is known to process information in the theta band frequency range (Cornwell, Johnson, Holroyd, Carver, & Grillon, 2008; Herweg, Solomon, & Kahana, 2020) and theta and gamma coupled activity has been identified in tinnitus patients in the parahippocampus (De Ridder, Congedo, & Vanneste, 2015; De Ridder & Vanneste, 2014; Mohan, Luckey, Weisz, & Vanneste, 2022). Understanding whether multisensory integration is involved in tinnitus and pain in the visual, vestibular, gustatory and olfactory cortex, in addition to auditory and somatosensory cortex, as previously shown, could be of high clinical relevance, as it may explain failures of existing treatments for tinnitus and pain, and lead to novel treatment approaches, such as multisensory cortex modulation or parahippocampal modulation, both for chronic pain and tinnitus.

2. Methods and materials

2.1. Subjects

For this study, a total of 150 participants were enrolled (mean age: 53.23 ± 11.02 years; 84 males, 66 females; all Caucasian), presenting at the neurosurgical clinic at Antwerp University hospital, Belgium. The healthy control group (N=50; mean age: 54.24 ± 10.21 years; 29 males, 21 females) had no reported history of neurological or neuropsychiatric disorders. Tinnitus subjects (N=50; mean age: 51.24 ± 12.93 years; 24 males, 26 females) underwent screening by a tinnitus specialist, excluding conditions like pulsatile tinnitus, Meniere's disease, otosclerosis, and chronic headache through standardized history taking. Meniere's disease was defined broadly as tinnitus with associated paroxysmal vertigo and/or low-frequency hearing loss (i.e., probable Meniere). Neurological disorders such as brain tumors were also ruled out, and all tinnitus patients had experienced tinnitus for over one year. Tinnitus was diagnosed if the patient perceived a sound for which no corresponding external sound source was present (De Ridder, Schlee, et al., 2021). Tinnitus patients had a tinnitus loudness of 5.67 (±2.74) as measured on a Visual Analogue Scale and distress level of 47.31 (±8.12) as measured using the Tinnitus Questionnaire. Pain patients (N=50; mean age: 53.76 ± 12.22 years; 31 males, 19 females) were screened by a pain specialist for neuropathic pain related to deafferentation (i.e., peripheral nerve, root, or central tract lesions) and ensured a duration of more than one year. Neuropathic pain was diagnosed clinically by the presence of the following characteristics: burning or electrical pain, numbness or hypoesthesia, paresthesias and allodynia. Pain patients had a tinnitus loudness of 6.01 (±1.94) as measured on a Visual Analogue Scale and distress level of 45.77 (±6.32) as measured using the Pain Vigilance and Awareness Questionnaire.

A comparison was made between the tinnitus and pain patients for age (F=1.42, $p = 0.81$) and gender ($\chi^2 = 0.17$, $p = 0.68$) revealing no significant effect between the two groups.

Co-morbidities such as anxiety and depression were not excluded. The study adhered to the ethical standards of the Helsinki declaration (1964) and the data were collected under the approval of IRB UZA OGA85. Data can be provided upon reasonable request.

2.2. EEG collection and processing

1. Data collection

Resting State EEGs were recorded on the same day pain and tinnitus scores were collected, following standard procedures, with subjects seated upright in a well-lit room with minimal background noise on a supportive chair. The resting state EEG recording lasted for approximatively 7 min, as to have at least 5 min of artefact free data for each participant after preprocessing. Recordings utilized Mitsar-201

amplifiers (NovaTech, https://www.novatecheeg.com/), capturing EEG signals from 19 electrodes arranged according to the 10–20 International system. Electrode impedances were confirmed to be below 5 kOhm. During data collection, participants kept their eyes closed, and the EEG signals were band-pass filtered between 0.15 and 200 Hz, with a sampling rate of 500 Hz. Patients were asked to abstain from alcohol and caffeine on the day of recording, as these are known to have immediate and significant effects on the central nervous system, leading to acute alterations in EEG patterns that could confound the study's results. Specifically, alcohol can depress neural activity, leading to a general slowing of EEG rhythms, while caffeine, a stimulant, can increase beta activity and overall arousal levels in the brain. These acute effects can introduce variability that obscures the EEG data's interpretation, making it difficult to isolate the neural phenomena of interest. In contrast, participants' regular drug regimens are typically prescribed to manage chronic conditions and are likely to have established effects on their neurophysiology. Abrupt discontinuation of these medications could induce withdrawal symptoms or destabilize the condition being managed, leading to significant physiological and psychological stress. This, in turn, could introduce variability in the EEG data far greater than that caused by the medications themselves. Moreover, chronic medications often lead to a relatively stable baseline state over time, which can be accounted for in the study's analysis, whereas the effects of acute abstinence could be unpredictable and detrimental to the participants' well-being. Therefore, the protocol aims to balance the need to minimize acute, confounding influences on EEG data with the ethical obligation to maintain participants' health and stability. By controlling for alcohol and caffeine while allowing the continuation of prescribed drug regimens, the study ensures that the recorded EEG patterns more accurately reflect the participants' typical neurophysiological state without introducing unnecessary risks.

To mitigate the risk of theta power amplification due to drowsiness, the participants' attentiveness was continually monitored by observing changes in the alpha rhythm and the presence of spindles in the EEG stream, indicative of drowsiness (Moazami-Goudarzi et al., 2010). Offline data processing included down-sampling to 128 Hz, bandpass filtering in the 2–44 Hz frequency range, and subsequent transfer to Eureka! Software (Congedo, 2002). The data were visually inspected for manual artifact rejection, removing episodic artifacts such as eye blinks, eye movements, teeth clenching, body movements, and ECG artifacts. Average Fourier cross-spectral matrices were computed for the delta (2–3.5 Hz), theta (4–7.5 Hz), alpha (8–12 Hz), beta (13–30 Hz), and gamma (30.5–44 Hz) frequency bands.

2. Source localization

Intracerebral sources were reconstructed through the use of standard low-resolution brain electromagnetic tomography (sLORETA). Prior to applying the sLORETA technique, a common average reference transformation (R. D. Pascual-Marqui, 2002) was performed as a standard procedure. Unlike methods assuming a predetermined number of active sources, sLORETA models electric neural activity as current density (A/m2). The lead-field matrix and solution space employed in this study were generated using the LORETA-Key program, available at no cost on https://www.uzh.ch/keyinst/loreta.htm. This software utilizes a lead field created with the boundary element approach to the MNI-152 and incorporates realistic electrode coordinates from the Montreal Neurological Institute, Canada.

The sLORETA-key anatomical template, based on probabilities from the Demon Atlas, subdivides and labels the neocortical (including the hippocampus and anterior cingulate cortex) MNI-152 space into 6,239 voxels of 5 mm3 dimensions. Co-registration involves the precise conversion between the Talairach and Tournoux space and the MNI-152 space.

3. Region of interest analysis

In our study, we estimated log-transformed electric current densities within the gamma frequency bands (30.5–44 Hz) for specific regions of interest (ROIs). These ROIs comprised the left and right auditory cortex, left and right somatosensory cortex, left and right visual cortex, left and right vestibular cortex, left and right olfactory cortex, and left and right gustatory cortex. The selection of these ROIs was guided by observed variations in activity identified in the whole-brain study. At each time step, the power in all 6,239 voxels was normalized to a power of 1 and then log-transformed. Consequently, for each frequency, the figures for the region of interest represent the log-transformed fraction of the overall power across all voxels. Utilizing a single voxel was chosen due to the 5 mm3 voxel size for each region of interest. The presence of volume conduction near the midline makes it challenging to distinguish laterality in these regions. The choice of these regions of interest and frequency bands aligns with our a priori hypothesis presented in the introduction, under the constraints of whole brain analysis (please refer to the introduction for details).

In order to prevent overlap between tinnitus and pain related to distress (anxiety, depression) common in both sensory disorders we excluded ROIs known to be involved in distress processing in these two disorders such as the dACC, insula, amygdala and OFC (Beebe Palumbo, Joos, De Ridder, & Vanneste, 2015; De Ridder et al., 2011a; De Ridder & Vanneste, 2021; De Ridder et al., 2011b; De Ridder et al., 2022a; De Ridder et al., 2022b; Joos, Vanneste, & De Ridder, 2012; van der Loo, Congedo, Vanneste, De Heyning, & De Ridder, 2011; Vanneste & De Ridder, 2013; Vanneste et al., 2010).

4. Lagged phase coherence

Typically, coherence and phase synchronization are interpreted as indicators of "connectivity" between time series associated with different regions of interest. However, the swift influence of volume conduction, a non-physiological input, significantly contaminates any measure of dependency (R. Pascual-Marqui, 2007b). To address this, Pascual-Marqui's approach (R. Pascual-Marqui, 2007a) introduces measurements of coherence and phase synchronization that selectively retain only non-instantaneous (delayed) connections, thus completely eliminating the confounding effect of volume conduction. The evaluation of "delayed phase coherence" between two sources provides insights into the extent of cross-talk between the regions generating the source activity (Congedo, John, De Ridder, Prichep, & Isenhart, 2010). Cross-talk can be conceptualized as information sharing through axonal transmission or neural message passing, as the two components oscillate coherently with a phase lag.

Specifically, the discrete Fourier transform decomposes the signal into a finite number of cosine and sine waves at the Fourier frequencies. The cosine waves lag behind their sine counterparts by a quarter of the period, inversely proportional to frequency. For example, a sinusoidal wave at 10 Hz has a period of 100 ms, with the sine lagged by 25 ms, or one-fourth of a cycle, in relation to the cosine. Lagged phase coherence thus reveals coherent oscillations with a delay of 25 ms at 10 Hz, 12.5 ms at 20 Hz, and so on. The threshold of significance for a specific lagged phase coherence value can be determined through asymptotic calculations, as outlined by Pascual-Marqui.

Linear coherence measures of the multivariate time series were also examined, with these non-negative measurements assuming a value of zero in cases of independence. Specifically, we investigated phase coherence between the left and right auditory cortex, left and right somatosensory cortex, left and right visual cortex, left and right vestibular cortex, left and right olfactory cortex, left and right gustatory cortex, and left and right parahippocampus for the theta frequency band.

2.3. Statistical analyses

1. Region of interest

We utilized log-transformed current density data from the gamma frequency band in the left and right auditory cortex, left and right somatosensory cortex, left and right visual cortex, left and right vestibular cortex, left and right olfactory cortex, and left and right gustatory cortex as dependent variables. The group categories (controls, tinnitus, and pain) served as independent variables in a MANOVA. We tested for normality using a Shapiro-Wilk test of normality. In case of a significant result and normally distributed in the MANOVA, separate univariate ANOVAs were conducted for each specific region. We tested for normality using a Shapiro-Wilk test of normality. To address the multiple univariate ANOVAs, we applied the Holm-Bonferroni multiple correction procedure (Holm, 1979).

2. Lagged phase coherence

Lagged phase coherence or the comparison of functional connectivity between patients with tinnitus and those without were computed for the theta frequency bands. The analysis was performed by means of the statistical non-parametric mapping methodology known as Fisher's permutation test (Nichols & Holmes, 2002), integrated with Holmes' non-parametric correction procedure for multiple comparisons (Holmes, Blair, Watson, & Ford, 1996). Comparisons were made between tinnitus and pain patients, as well as between tinnitus and controls and pain and controls. In this case, a "t-statistic on Log transformed data" test was chosen, with a variance smoothing parameter of 0 and a number of randomizations of 5,000. The test allowed to calculate the threshold values in terms of "log F-ratio" and yielded to a file containing the computed extremes of probability (ExtremePs), the corresponding maximal thresholds, and the thresholds at probability values of $p < 0.01$ and $p < 0.05$, with $p < 0.05$ being indicative of statistical significance (Friston, Frith, Liddle, & Frackowiak, 1991).

3. Results

3.1. Region of interest analyses

To characterise the differences between chronic tinnitus and neuropathic pain, we conducted a region of interest analysis for the gamma frequency band including the left and right auditory cortex, the left and right somatosensory cortex, the left and right visual cortex, the left and right vestibular cortex, the left and right olfactory cortex and the left and right gustatory cortex. The selection of this specific frequency bands and regions of interest was based on our hypothesis.

A MANOVA of the log-transformed current density for the left and right auditory cortex, the left and right somatosensory cortex, the left and right visual cortex, the left and right vestibular cortex, the left and right olfactory cortex and the left and right gustatory cortex as dependent variables and group (controls, tinnitus, and pain) as independent variables for the gamma frequency band showed an overall effect (F=6.95, $p < 0.001$, $\eta^2 = 0.38$; see Fig. 1). An univariate ANOVA revealed a significant effect in the left and right auditory cortex (see Fig. 1a,b; Table 1), the left and right somatosensory cortex (see Fig. 1c,d; Table 1), left and right visual cortex (see Fig. 1e,f; Table 1), the left and right vestibular cortex (see Fig. 1g,h; Table 1), but not for the left and

Table 1
Univariate ANOVA for left and right auditory cortex, the left and right somatosensory cortex, the left and right visual cortex, the left and right vestibular cortex, the left and right olfactory cortex and the left and right gustatory cortex.

Area	Side	F	p	η^2
Auditory cortex	L	12.93	< 0.001	0.15
	R	5.04	0.008	0.06
Somatosensory cortex	L	13.24	< 0.001	0.15
	R	14.34	0.001	0.16
Visual cortex	L	4.99	0.008	0.06
	R	7.75	0.001	0.10
Vestibular cortex	L	7.55	0.001	0.09
	R	6.49	0.002	0.08
Olfactory cortex	L	0.40	0.67	
	R	0.93	0.40	
Gustatory cortex	L	1.32	0.27	
	R	2.04	0.13	

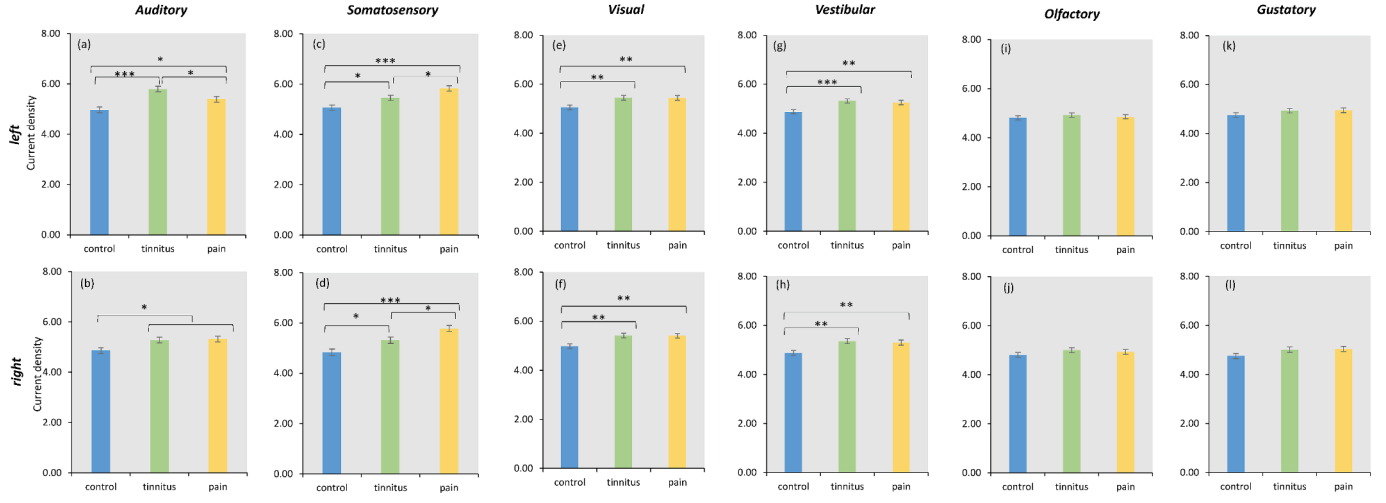


Fig. 1. Gamma band current density for tinnitus and pain subjects in comparison to controls in different sensory cortices. (a-b) Tinnitus subjects demonstrated increased gamma current density in the left auditory cortex in comparison to pain subjects. No significant difference was revealed between tinnitus and pain subjects for the right auditory cortex. (c-d) For both the left and right somatosensory cortex, increased current density is identified in both pain and tinnitus subjects in comparison to controls. Pain subjects had increased current density in comparison to tinnitus subjects. (e-f) Tinnitus and pain subjects show increased gamma current density in left and right visual cortex in comparison to controls. No difference in gamma current density was identified between tinnitus and pain subjects. (g,h) For left and right vestibular cortex, tinnitus and pain subjects demonstrate increased gamma current density in comparison to controls. No significant difference was found between tinnitus and pain subjects. (i-k) No significant differences in gamma current density are identified in the left and right olfactory cortex as well as for the left and right gustatory cortex between tinnitus, pain and control subjects. * $p < 0.05$; ** $p < 0.01$, *** $p < 0.001$.

right olfactory cortex (see Fig. 1i,j; Table 1) and the left and right gustatory cortex (see Fig. 1k,l; Table 1).

For the left auditory cortex, a pairwise comparison revealed an increased current density for tinnitus and pain subjects in comparison to controls. Tinnitus subjects had increased current density for the left auditory cortex in comparison to pain subjects. For the right auditory cortex, a pairwise comparison yielded a significantly increased current density for tinnitus and pain subjects in comparison to controls. No significant difference was revealed between tinnitus and pain subjects for the right auditory cortex. See Table 2 for a statistical overview.

For both the left and right somatosensory cortex, a pairwise comparison revealed an increased current density for pain and tinnitus subjects in comparison to controls. Pain subjects had increased current density for the left somatosensory cortex in comparison to tinnitus subjects. See Table 2 for a statistical overview.

For left and right visual cortex, a pairwise comparison revealed an increased current density for tinnitus and pain subjects in comparison to controls. No significant difference was obtained between tinnitus and pain subjects. See Table 2 for a statistical overview.

For left and right vestibular cortex, a pairwise comparison revealed an increased current density for tinnitus and pain subjects in comparison to controls. No significant difference was obtained between tinnitus and pain subjects. See Table 2 for a statistical overview.

3.2. Functional connectivity

1. Tinnitus *vs.* Control subjects

A comparison between tinnitus and control subjects revealed significantly increased functional connectivity between the left and right auditory cortex as well as between the left and right somatosensory cortex, and the left and right parahippocampus for tinnitus subjects in comparison to control subjects (F=5.21, $p < 0.05$). Furthermore, increased functional connectivity was seen between left auditory cortex and the left parahippocampus, the left somatosensory cortex and the left parahippocampus, the left visual cortex and the left parahippocampus, and the left vestibular cortex and the left parahippocampus for the theta frequency band for the tinnitus subjects. Similar differences in connectivity were revealed for the right hemisphere between the auditory cortex, somatosensory, visual, vestibular corte and parahippocampus for the theta frequency band. See Fig. 2 for overview.

2. Pain *vs.* Control subjects

A comparison between pain and control subjects revealed significantly increased functional connectivity between the left and right somatosensory cortex, the left and right auditory cortex, left and right parahippocampus for pain subjects in comparison to control subjects (F=5.21, $p < 0.05$). Furthermore, increased functional connectivity was seen between left auditory cortex and the left parahippocampus, the left somatosensory cortex and the left parahippocampus, the left visual cortex and the left parahippocampus, and the left vestibular cortex and the left parahippocampus for the theta frequency band for the pain subjects. Similar differences in connectivity were revealed for the right hemisphere between the somatosensory auditory, visual, vestibular cortex and parahippocampus for the theta frequency band. See Fig. 2 for overview.

3. Conjunction between Pain and Tinnitus subjects

A conjunction between neuropathic pain and tinnitus after subtraction controls yielded a significant effect for the theta frequency band (Z=6.03, $p < 0.05$). That is, a significant commonly increased functional connectivity between the left and right somatosensory cortex, the left and right auditory cortex, left and right parahippocampus for pain and tinnitus subjects in comparison to control subjects (F=5.21, $p < 0.05$). Furthermore, increased theta functional connectivity was seen between the left auditory cortex and the left parahippocampus, the left somatosensory cortex and the left parahippocampus, the left visual cortex and the left parahippocampus, and the left vestibular cortex and the left parahippocampus. Similar commonalities in connectivity were revealed for the right hemisphere between the somatosensory auditory, visual, vestibular cortex and parahippocampus for the theta frequency band. See Fig. 2 for overview.

4. Discussion

Three main questions are presented in the introduction. 1. From a Bayesian brain perspective, is the prediction error, as reflected by gamma band activity, only computed in the deafferented auditory cortex in tinnitus, and somatosensory cortex in pain, or does auditory and somatosensory deafferentation also result in prediction errors in the other sensory cortices, such as the visual, somatosensory, vestibular, gustatory and olfactory cortex due to discrepancies between expected auditory and expected associated visual, somatosensory, vestibular and other stimuli? 2. How do the different sensory cortices interact in chronic pain and tinnitus? Do they interact directly between themselves, or do they communicate indirectly via the contextual multisensory integration mechanism of the parahippocampus?

This study shows that in chronic pain and tinnitus all sensory cortices (somatosensory, auditory, visual vestibular) except olfactory and gustatory cortex are characterized by increased gamma band activity, and that these sensory cortices (somatosensory, auditory, visual vestibular) are functionally connected to the parahippocampal cortex, but not directly to each other.

From a Bayesian brain perspective, the auditory deafferentation

Table 2
Pairwise comparison between tinnitus, pain and control subjects for left and right auditory cortex, the left and right somatosensory cortex, the left and right visual cortex, the left and right vestibular cortex.

		Tinnitus vs Pain			*Tinnitus vs Control*			*Pain vs Control*		
Area	**Side**	***F***	***p***	η^2	***F***	***p***	η^2	***F***	***p***	η^2
Auditory cortex	L	6.18	0.014	0.04	25.85	< 0.001	0.15	6.76	0.010	0.04
	R	0.06	0.81	0.001	6.86	0.010	0.05	8.21	0.005	0.05
Somatosensory cortex	L	6.90	0.010	0.05	6.37	0.013	0.04	26.45	< 0.001	0.15
	R	6.99	0.009	0.05	7.35	0.008	0.05	26.68	< 0.001	0.16
Visual cortex	L	0.004	0.95		7.67	0.006	0.05	7.31	0.008	0.047
	R	0.001	0.98		11.65	0.001	0.07	11.47	0.001	0.07
Vestibular cortex	L	0.34	0.56		13.09	< 0.001	0.08	9.22	0.003	0.06
	R	0.21	0.65		11.04	0.001	0.07	8.24	0.005	0.05

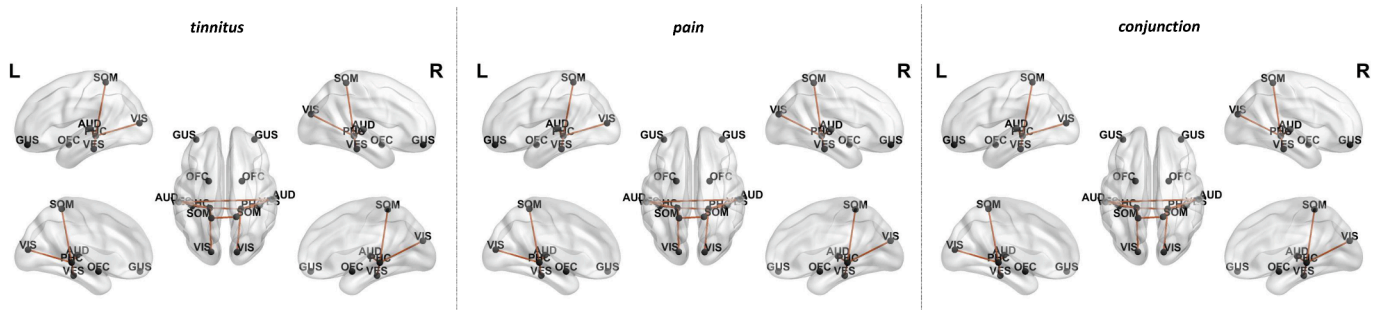


Fig. 2. Functional connectivity as measured by lagged phase synchronization. Left figure: A comparison between tinnitus and control subjects revealed significantly increased functional connectivity bilaterally between the left and right auditory cortices as well as the left and right somatosensory cortices and the left and right parahippocampal cortices, but also bilaterally between the ipsilateral auditory cortex, somatosensory cortex, vestibular cortex, visual cortex respectively and the ipsilateral parahippocampus for tinnitus subjects in comparison to control subjects for the theta frequency band. Middle figure: A comparison between pain and control subjects demonstrated significantly increased functional connectivity bilaterally between the left and right auditory, left and right somatosensory and left and right parahippocampal cortices, as well as between the ipsilateral auditory cortex, somatosensory cortex, vestibular cortex, visual cortex respectively and the ipsilateral parahippocampus for pain subjects in comparison to control subjects for the theta frequency band. Right figure: A conjunction between neuropathic pain and tinnitus after subtraction of controls yielded a significant common effect for the theta frequency band. Increased common theta functional connectivity is identified bilaterally between the left and right auditory, left and right somatosensory and left and right parahippocampal cortices, as well as between the ipsilateral auditory cortex, somatosensory corteex, vestibular cortex, visual cortex respectively and the ipsilateral parahippocampus for tinnitus subjects and neuropathic pain subjects.

leads to a prediction error, as reflected by gamma band activity (Arnal et al., 2011; Cao et al., 2017; Chao et al., 2018; Durai, Sanders, Kobayashi, & Searchfield, 2019; Mohan, De Ridder, & Vanneste, 2016; Mohan et al., 2022; Sedley et al., 2016), in the auditory cortex, leading to an incongruence between expected stimuli in other sensory domains. This incongruence seems to be mediated via the parahippocampal area, as all sensory cortices communicate to the parahippocampal area, but not directly between the sensory cortices themselves. This communication (i.e., functional connectivity) also occurs in the gamma band, suggesting that the bottom-up prediction error in one domain is transmitted to the parahippocampus, where it is compared to information coming from other sensory areas for multisensory integration. If there is a discrepancy that persists this may lead to filling in the expected missing information, based on the input from the deafferented sensory domain, as well as the other sensory domains. As the gamma activity is present throughout the 5 min recording, this suggests that indeed the prediction errors, i.e. the discrepancy persists.

From these data it appears that the brain may perform a kind of 'duck test' and fill in the expected auditory information based on the information from other sensory domains, rather than solely by comparing topographic thalamocortical column activity within one sensory domain (De Ridder et al., 2014b). This may explain the beneficial effect of introducing congruence between senses, as used in mirror treatment for phantom pain, in which a mirror is used to introduce a visual trick by which the missing limb is seen as a mirror image of the persisting contralateral limb (Ramachandran & Rogers-Ramachandran, 1996). Mirror therapy is the most efficacious (short-term) treatment for phantom pain, as shown by a network *meta*-analysis (J. Wang, Fan, Gc, & Zhao, 2022; Xie et al., 2022), yet doubts persist about its long term efficacy (Makin, 2021). Similarly, an auditory mirror therapy device has been developed that consists of a modified ear defender device with microphones that swaps sounds from left pinna to the right ear canal and from the right pinna to the left ear canal (Linnman, 2022). Analogous to the benefit of the mirror in phantom pain the auditory mirror device is capable of reducing both loudness and distress in tinnitus with hearing loss (Linnman, 2022).

Another related question is whether failures to treat pain and tinnitus in half of patients by implants on the somatosensory cortex (De Ridder et al., 2007a; De Ridder et al., 2007b; De Ridder, Vanneste, Van Laere, & Menovsky, 2013) and auditory cortex (Claes, Stamberger, Van de Heyning, De Ridder, & Vanneste, 2014; De Ridder, De Mulder, Menovsky, et al., 2007; De Ridder, De Mulder, Verstraeten, Seidman, et al., 2007; De Ridder et al., 2006; De Ridder et al., 2004; De Ridder, Menovsky, & van de Heyning, 2008) respectively can be attributed to the persisting parahippocampal maintenance of the phantom percept, being fed information by the other sensory cortices? Indirect support for this concept comes from a study in which failures of auditory cortex implants for tinnitus were analyzed by source-localized EEG. Performing a whole brain analysis, it was shown that the difference between responders and non-responders was characterized by increased gamma band activity in the parahippocampal area. Furthermore, functional connectivity between the implant area, i.e. the auditory cortex, and the parahippocampus was identified as essential for treatment success (De Ridder & Vanneste, 2014). This suggests that even though the electrode was placed on the auditory cortex, its main treatment effect involved modification of the gamma band activity in the parahippocampal area (De Ridder & Vanneste, 2014). This is in keeping with the findings of this study, that shows the pivotal role of the parahippocampal area in integrating the prediction errors from the different sensory domains.

It is curious that there seem two separate sensory groups. On the one hand the visual, vestibular, somatosensory and auditory domains, that communicate to the parahippocampus and are all involved in multisensory integration in pain and tinnitus, and on the other hand the olfactory and gustatory system, that are not involved. There are multiple possible explanations for this dichotomy. On the one hand the cartesian coordinates of the olfactory and gustatory cortex selected in this study may be wrong. This is less likely, as the XYZ coordinates of all the sensory cortices were selected based on a neurosynth *meta*-analysis.

Another reason may be that the chemical senses are differently wired. The limbic and paralimbic areas have been divided into olfactocentric and hippocampocentric groups (Catani & Thiebaut de Schotten, 2012; Mega, Cummings, Salloway, & Malloy, 1997; Mesulam, 2000). The olfactocentric division is organized around the olfactory piriform cortex and includes the orbitofrontal, insular and temporopolar area, and as such the gustatory insula (Catani & Thiebaut de Schotten, 2012; Mega et al., 1997; Mesulam, 2000). The hippocampocentric division is organized around the hippocampus and includes the parahippocampus and posterior cingulate cortex (Catani & Thiebaut de Schotten, 2012; Mega et al., 1997; Mesulam, 2000). They overlap in the rostral and dorsal anterior cingulate cortex. Thus it is likely that the phylogenetically older chemical senses and the more recent other senses do differ in their integration mechanisms, the older via the insula, the more recent via the (para)hippocampus.

A weakness of the study is that the participants' pain medication was

not stopped before the EEG. Even though this may influence the EEG, we believe this does not impact the results of this study, as we are not looking for differences, but for commonalities between tinnitus and pain. Medication may exacerbate differences, but is unlikely to influence commonalities between the groups, as patients are taking different medication regimens.

A second weakness of the study is that neither for the neuropathic pain, nor for the tinnitus group a control group is incorporated that does not present with typical deafferentation symptoms, i.e. numbness/hypoesthesia for the neuropathic pain group, and no hearing loss for the tinnitus group. Apart from the difficulty of finding people that belong to such a control group, it is also questionable whether it makes sense from a Bayesian brain perspective. For example, it has been shown that tinnitus without hearing loss does not exclude auditory deafferentation (Weisz, Hartmann, Dohrmann, Schlee, & Norena, 2006), and similarly covid can cause asymptomatic axonal or demyelinating changes in peripheral nerves confirmed by electroneurography, i.e. deafferentation without hypoesthesia or pain (Schirinzi et al., 2021).

In conclusion, pain and tinnitus are associated with prediction errors in all sensory cortices except the olfactory and gustatory cortex. The different senses may create a unified integrated percept via the parahippocampal 'context' area (E. Aminoff et al., 2007; E. M. Aminoff et al., 2013), and when one sensory domain is deprived, the other senses may provide the parahippocampal area with the most likely sound or somatosensory sensation to fill in the gap, applying a duck test approach. This novel concept paves the way to develop novel treatments for pain and tinnitus, using multisensory modulation or via parahippocampal targeting. In tinnitus the auditory cortex has been targeted with non-invasive transcranial magnetic stimulation(Dong et al., 2020; Lefebvre-Demers, Doyon, & Fecteau, 2020; Liang et al., 2020; Soleimani, Jalali, & Hasandokht, 2016), transcranial direct current stimulation (Lefebvre-Demers et al., 2020; Martins et al., 2022; Song et al., 2012b; T. C. Wang et al., 2018), transcranial alternating current stimulation (Claes et al., 2014; Vanneste et al., 2013a; Vanneste et al., 2013b) and transcranial random noise stimulation (Claes et al., 2014; Joos, De Ridder, & Vanneste, 2015; To, Ost, Hart, De Ridder, & Vanneste, 2017; Vanneste et al., 2013a), as well as surgical implants on the secondary and primary auditory cortex (De Ridder et al., 2006; De Ridder et al., 2004). Whereas this has yielded some benefit in tinnitus loudness reduction in individual studies, at a *meta*-analytic level no tinnitus loudness reduction can be identified with rTMS of the auditory cortex. For tDCS a *meta*-analysis has shown that a small tinnitus loudness reduction can be achieved, albeit smaller than the minimal clinically important difference (Martins et al., 2022) and thus clinically irrelevant. These results are in contrast to what would be expected if the auditory cortex is the sole and exclusive tinnitus generator. Based on the concept of network science a theoretical explanation for this treatment failure has been provided by explaining that tinnitus is an emergent property of a tinnitus network (De Ridder, Vanneste, Weisz, et al., 2014c; Schlee, Hartmann, Langguth, & Weisz, 2009). The proposed tinnitus network incorporates many non-auditory areas (Elgoyhen, Langguth, De Ridder, & Vanneste, 2015; Vanneste & De Ridder, 2012), but up to now has never considered the involvement of other sensory areas as compensation. Similarly, pain has been proposed as an emergent property of a pain network (De Ridder, Adhia, et al., 2021; De Ridder, Elgoyhen, et al., 2011; Vanneste & De Ridder, 2021), and somatosensory cortex implants have been performed to treat neuropathic pain (De Ridder, De Mulder, Verstraeten, Sunaert, et al., 2007c), also with some benefit, yet also not universal. Based on the results of this study one could propose to apply desynchronizing transcranial noise stimulation (Adhia et al., 2022; De Ridder, Siddiqi, Dauwels, Serdijn, & Strydis, 2024) of the different sensory cortices (vestibular, somatosensory, auditory, visual), as to remove to multisensory congruent evidence that appears to be critical in generating the Bayesian posterior belief, i.e. the pain and tinnitus. Considering the central hub function of the parahippocampus in this and previous studies (Berger et al., 2024; De Ridder et al., 2023), this structure may be incorporated into the stimulation design. Indirect evidence that the parahippocampus is critical in treatment success is offered via an imaging study that demonstrates auditory cortex stimulation is only effective if the auditory cortex is functionally connected to the parahippocampus (De Ridder & Vanneste, 2014). In summary, this study may lead to the development of new neuromodulation approaches for tinnitus and pain.

CRediT authorship contribution statement

Dirk De Ridder: Writing – review & editing, Writing – original draft, Conceptualization. **Divya Adhia:** Writing – review & editing, Writing – original draft. **Sven Vanneste:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization.

Data availability

The authors do not have permission to share data.

Acknowledgements

The authors want to thank John Ward, philantropist, and Tinnitus Quest, both for their generous support in sponsoring this work.

References

Adhia, D., Mathew, J., Vanneste, S., Mani, R., & De Ridder, D. (2022). High-definition transcranial infraslow pink noise stimulation can influence functional and effective cortical connectivity in individuals with chronic low back pain: A pilot randomized placebo-controlled study. *Neuromodulation, in press*.

Ahveninen, J., Lee, H.J., Yu, H.Y., Lee, C.C., Chou, C.C., Ahlfors, S.P., Lin, F.H., 2024. Visual stimuli modulate local field potentials but drive no high-frequency activity in human auditory cortex. J. Neurosci. 44 (7) https://doi.org/10.1523/JNEUROSCI.0890-23.2023.

Alain, C., Woods, D.L., Knight, R.T., 1998. A distributed cortical network for auditory sensory memory in humans. Brain Res. 812 (1–2), 23–37.

Albanese, M.C., Duerden, E.G., Rainville, P., Duncan, G.H., 2007. Memory traces of pain in human cortex. J. Neurosci. 27 (17), 4612–4620, 27/17/4612 [pii] 10.1523/JNEUROSCI.0695-07.2007.

Allman, B.L., Bittencourt-Navarrete, R.E., Keniston, L.P., Medina, A.E., Wang, M.Y., Meredith, M.A., 2008. Do cross-modal projections always result in multisensory integration? Cereb. Cortex 18 (9), 2066–2076. https://doi.org/10.1093/cercor/bhm230.

Aminoff, E., Gronau, N., Bar, M., 2007. The parahippocampal cortex mediates spatial and nonspatial associations. Cereb. Cortex 17 (7), 1493–1503. https://doi.org/10.1093/cercor/bhl078.

Aminoff, E.M., Kveraga, K., Bar, M., 2013. The role of the parahippocampal cortex in cognition. Trends Cogn. Sci. 17 (8), 379–390. https://doi.org/10.1016/j.tics.2013.06.009.

Arnal, L.H., Wyart, V., Giraud, A.L., 2011. Transitions in neural oscillations reflect prediction errors generated in audiovisual speech. Nat. Neurosci. 14 (6), 797–801 nn.2810 [pii] 10.1038/nn.2810.

Auksztulewicz, R., Friston, K.J., Nobre, A.C., 2017. Task relevance modulates the behavioural and neural effects of sensory predictions. PLoS Biol. 15 (12), e2003143.

Bar, M., Aminoff, E., Ishai, A., 2008a. Famous faces activate contextual associations in the parahippocampal cortex. Cereb. Cortex 18 (6), 1233–1238 bhm170 [pii] 10.1093/cercor/bhm170.

Bar, M., Aminoff, E., Schacter, D.L., 2008b. Scenes unseen: the parahippocampal cortex intrinsically subserves contextual associations, not scenes or places per se. J. Neurosci. 28 (34), 8539–8544, 28/34/8539 [pii] 10.1523/JNEUROSCI.0987-08.2008.

Basura, G.J., Koehler, S.D., Shore, S.E., 2012. Multi-sensory integration in brainstem and auditory cortex. Brain Res. 1485, 95–107. https://doi.org/10.1016/j.brainres.2012.08.037.

Baumann, O., Mattingley, J.B., 2016. Functional organization of the parahippocampal cortex: dissociable roles for context representations and the perception of visual scenes. J. Neurosci. 36 (8), 2536–2542. https://doi.org/10.1523/JNEUROSCI.3368-15.2016.

Beebe Palumbo, D., Joos, K., De Ridder, D., Vanneste, S., 2015. The management and outcomes of pharmacological treatments for tinnitus. Curr. Neuropharmacol. 13 (5), 692–700.

Berger, J.I., Billig, A.J., Sedley, W., Kumar, S., Griffiths, T.D., Gander, P.E., 2024. What is the role of the hippocampus and parahippocampal gyrus in the persistence of tinnitus? Hum. Brain Mapp. 45 (3), e26627.

Bodner, M., Kroger, J., Fuster, J.M., 1996. Auditory memory cells in dorsolateral prefrontal cortex. Neuroreport 7 (12), 1905–1908.

Cao, L., Thut, G., Gross, J., 2017. The role of brain oscillations in predicting self-generated sounds. Neuroimage 147, 895–903. https://doi.org/10.1016/j.neuroimage.2016.11.001.
Catani, M., Thiebaut de Schotten, M., 2012. Limbic System *Atlas of Human Connections*. Oxford Oxford University Press, pp. 443–444.
Chao, Z.C., Takaura, K., Wang, L., Fujii, N., Dehaene, S., 2018. Large-scale cortical networks for hierarchical prediction and prediction error in the primate brain. Neuron 100 (5), 1252–1266 e1253. https://doi.org/10.1016/j.neuron.2018.10.004.
Chen, Y.C., Wang, F., Wang, J., Bo, F., Xia, W., Gu, J.P., Yin, X., 2017. Resting-state brain abnormalities in chronic subjective tinnitus: a meta-analysis. Front. Hum. Neurosci. 11, 22. https://doi.org/10.3389/fnhum.2017.00022.
Claes, L., Stamberger, H., Van de Heyning, P., De Ridder, D., Vanneste, S., 2014. Auditory cortex tACS and tRNS for tinnitus: single versus multiple sessions. Neural Plast. 2014, 436713 https://doi.org/10.1155/2014/436713.
Congedo, M., 2002. EureKa! (Version 3.0) [Computer Software]. NovaTech EEG Inc., Knoxville, TN. Freeware available at.
Cornwell, B.R., Johnson, L.L., Holroyd, T., Carver, F.W., Grillon, C., 2008. Human hippocampal and parahippocampal theta during goal-directed spatial navigation predicts performance on a virtual Morris water maze. J. Neurosci. 28 (23), 5983–5990. https://doi.org/10.1523/JNEUROSCI.5001-07.2008.
De Ridder, D., De Mulder, G., Walsh, V., Muggleton, N., Sunaert, S., Moller, A., 2004. Magnetic and electrical stimulation of the auditory cortex for intractable tinnitus. Case Report. *J Neurosurg* 100 (3), 560–564.
De Ridder, D., De Mulder, G., Verstraeten, E., Van der Kelen, K., Sunaert, S., Smits, M., Moller, A.R., 2006. Primary and secondary auditory cortex stimulation for intractable tinnitus. ORL J. Otorhinolaryngol Relat. Spec. 68 (1), 48–54; discussion 54–45.
De Ridder, D., De Mulder, G., Verstraeten, E., Seidman, M., Elisevich, K., Sunaert, S., Moller, A., 2007b. Auditory cortex stimulation for tinnitus. Acta Neurochir. Suppl. 97 (Pt 2), 451–462. https://doi.org/10.1007/978-3-211-33081-4_52.
De Ridder, D., Vanneste, S., 2014. Targeting the parahippocampal area by auditory cortex stimulation in tinnitus. Brain Stimul. https://doi.org/10.1016/j.brs.2014.04.004.
De Ridder, D., De Mulder, G., Menovsky, T., Sunaert, S., Kovacs, S., 2007a. Electrical stimulation of auditory and somatosensory cortices for treatment of tinnitus and pain. Prog. Brain Res. 166, 377–388. S0079-6123(07)66036-1 [pii] 10.1016/S0079-6123(07)66036-1.
De Ridder, D., Vanneste, S., 2021. The Bayesian brain in imbalance: medial, lateral and descending pathways in tinnitus and pain: a perspective. Prog. Brain Res. 262, 309–334. https://doi.org/10.1016/bs.pbr.2020.07.012.
De Ridder, D., De Mulder, G., Verstraeten, E., Sunaert, S., Moller, A., 2007c. Somatosensory cortex stimulation for deafferentation pain. Acta Neurochir. Suppl. 97 (Pt 2), 67–74.
De Ridder, D., Menovsky, T., van de Heyning, P., 2008. Auditory cortex stimulation for tinnitus suppression. Otol. Neurotol. 29 (4), 574–575. https://doi.org/10.1097/MAO.0b013e3181719773 author reply 575.
De Ridder, D., Elgoyhen, A.B., Romo, R., Langguth, B., 2011a. Phantom percepts: tinnitus and pain as persisting aversive memory networks. PNAS 108 (20), 8075–8080, 1018466108 [pii] 10.1073/pnas.1018466108.
De Ridder, D., Vanneste, S., Congedo, M., 2011b. The distressed brain: a group blind source separation analysis on tinnitus. PLoS One 6 (10), e24273.
De Ridder, D., Vanneste, S., Van Laere, K., Menovsky, T., 2013. Chasing map plasticity in neuropathic pain. World Neurosurg. 80 (6) https://doi.org/10.1016/j.wneu.2012.12.009, 901 e901–905.
De Ridder, D., Joos, K., Vanneste, S., 2014a. The enigma of the tinnitus-free dream state in a Bayesian world. Neural Plast. 2014, 612147 https://doi.org/10.1155/2014/612147.
De Ridder, D., Vanneste, S., Freeman, W., 2014b. The Bayesian brain: phantom percepts resolve sensory uncertainty. Neurosci. Biobehav. Rev. 44, 4–15. https://doi.org/10.1016/j.neubiorev.2012.04.001.
De Ridder, D., Vanneste, S., Weisz, N., Londero, A., Schlee, W., Elgoyhen, A.B., Langguth, B., 2014c. An integrative model of auditory phantom perception: tinnitus as a unified percept of interacting separable subnetworks. Neurosci. Biobehav. Rev. 44, 16–32. https://doi.org/10.1016/j.neubiorev.2013.03.021.
De Ridder, D., Congedo, M., Vanneste, S., 2015. 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., 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., Schlee, W., Vanneste, S., Londero, A., Weisz, N., Kleinjung, T., 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., Smith, M., Adhia, D., 2022a. Pain and the triple network model. Front. Neurol. 13, 757241 https://doi.org/10.3389/fneur.2022.757241.
De Ridder, D., Vanneste, S., Song, J.J., Adhia, D., 2022b. Tinnitus and the triple network model: a perspective. Clin Exp Otorhinolaryngol. https://doi.org/10.21053/ceo.2022.00815.
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., Siddiqi, M.A., Dauwels, J., Serdijn, W.A., Strydis, C., 2024. NeuroDots: from single-target to brain-network modulation: why and what is needed? Neuromodulation. https://doi.org/10.1016/j.neurom.2024.01.003.
Diaconescu, A.O., Alain, C., McIntosh, A.R., 2011. The co-occurrence of multisensory facilitation and cross-modal conflict in the human brain. J. Neurophysiol. 106 (6), 2896–2909. https://doi.org/10.1152/jn.00303.2011.
Dong, C., Chen, C., Wang, T., Gao, C., Wang, Y., Guan, X., Dong, X., 2020. Low-frequency repetitive transcranial magnetic stimulation for the treatment of chronic tinnitus: a systematic review and meta-analysis of randomized controlled trials. Biomed Res. Int. 2020, 3141278. https://doi.org/10.1155/2020/3141278.
Durai, M., Sanders, M., Kobayashi, K., Searchfield, G.D., 2019. Auditory streaming and prediction in tinnitus sufferers. Ear Hear. 40 (2), 345–357. https://doi.org/10.1097/AUD.0000000000000620.
Eichenbaum, H., Lipton, P.A., 2008. Towards a functional organization of the medial temporal lobe memory system: role of the parahippocampal and medial entorhinal cortical areas. Hippocampus 18 (12), 1314–1324. https://doi.org/10.1002/hipo.20500.
Elgoyhen, A.B., Langguth, B., De Ridder, D., Vanneste, S., 2015. Tinnitus: perspectives from human neuroimaging. Nat. Rev. Neurosci. 16 (10), 632–642. https://doi.org/10.1038/nrn4003.
Engelien, A., Stern, E., Isenberg, N., Engelien, W., Frith, C., Silbersweig, D., 2000. The parahippocampal region and auditory-mnemonic processing. Ann. N. Y. Acad. Sci. 911, 477–485.
Foxe, J.J., Morocz, I.A., Murray, M.M., Higgins, B.A., Javitt, D.C., Schroeder, C.E., 2000. Multisensory auditory-somatosensory interactions in early cortical processing revealed by high-density electrical mapping. Brain Res. Cogn. Brain Res. 10 (1–2), 77–83.
Foxe, J.J., Wylie, G.R., Martinez, A., Schroeder, C.E., Javitt, D.C., Guilfoyle, D., Murray, M.M., 2002. Auditory-somatosensory multisensory processing in auditory association cortex: an fMRI study. J. Neurophysiol. 88 (1), 540–543.
Friston, K.J., Frith, C.D., Liddle, P.F., Frackowiak, R.S., 1991. Comparing functional (PET) images: the assessment of significant change. J. Cereb. Blood Flow Metab. 11 (4), 690–699. https://doi.org/10.1038/jcbfm.1991.122.
Gueguen, M.C.M., Lopez-Persem, A., Billeke, P., Lachaux, J.P., Rheims, S., Kahane, P., Bastin, J., 2021. Anatomical dissociation of intracerebral signals for reward and punishment prediction errors in humans. Nat. Commun. 12 (1), 3344. https://doi.org/10.1038/s41467-021-23704-w.
Herweg, N.A., Solomon, E.A., Kahana, M.J., 2020. Theta oscillations in human memory. Trends Cogn. Sci. 24 (3), 208–227. https://doi.org/10.1016/j.tics.2019.12.006.
Holm, S., 1979. A simple sequential rejective multiple test procedure. Scand. J. Stat. 6, 65–70.
Holmes, A.P., Blair, R.C., Watson, J.D., Ford, I., 1996. Nonparametric analysis of statistic images from functional mapping experiments. J. Cereb. Blood Flow Metab. 16 (1), 7–22. https://doi.org/10.1097/00004647-199601000-00002.
Joos, K., Vanneste, S., De Ridder, D., 2012. Disentangling depression and distress networks in the tinnitus brain. PLoS One 7 (7), e40544.
Joos, K., De Ridder, D., Vanneste, S., 2015. The differential effect of low- versus high-frequency random noise stimulation in the treatment of tinnitus. Exp. Brain Res. 233 (5), 1433–1440. https://doi.org/10.1007/s00221-015-4217-9.
Kayser, C., Petkov, C.I., Augath, M., Logothetis, N.K., 2007. Functional imaging reveals visual modulation of specific fields in auditory cortex. J. Neurosci. 27 (8), 1824–1835. https://doi.org/10.1523/JNEUROSCI.4737-06.2007.
Klostermann, E.C., Kane, A.J., Shimamura, A.P., 2008. Parietal activation during retrieval of abstract and concrete auditory information. Neuroimage 40 (2), 896–901. S1053-8119(07)01137-8 [pii] 10.1016/j.neuroimage.2007.10.068.
Lee, S.Y., Nam, D.W., Koo, J.W., De Ridder, D., Vanneste, S., Song, J.J., 2017. No auditory experience, no tinnitus: lessons from subjects with congenital- and acquired single-sided deafness. Hear. Res. 354, 9–15. https://doi.org/10.1016/j.heares.2017.08.002.
Lefebvre-Demers, M., Doyon, N., Fecteau, S., 2020. Non-invasive neuromodulation for tinnitus: a meta-analysis and modeling studies. Brain Stimul. 14 (1), 113–128. https://doi.org/10.1016/j.brs.2020.11.014.
Lewis, A.G., Bastiaansen, M., 2015. A predictive coding framework for rapid neural dynamics during sentence-level language comprehension. Cortex 68, 155–168. https://doi.org/10.1016/j.cortex.2015.02.014.
Liang, Z., Yang, H., Cheng, G., Huang, L., Zhang, T., Jia, H., 2020. Repetitive transcranial magnetic stimulation on chronic tinnitus: a systematic review and meta-analysis. BMC Psychiatry 20 (1), 547. https://doi.org/10.1186/s12888-020-02947-9.
Linnman, C., 2022. Auditory mirror therapy for tinnitus: a pilot study. J. Am. Acad. Audiol. 33 (4), 220–223. https://doi.org/10.1055/s-0042-1743548.
Makin, T.R., 2021. Phantom limb pain: thinking outside the (mirror) box. Brain 144 (7), 1929–1932. https://doi.org/10.1093/brain/awab139.
Martins, M.L., Souza, D.D.S., Cavalcante, M., Barboza, H.N., de Medeiros, J.F., Dos Santos Andrade, S.M.M., 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.
Meerwijk, E.L., Ford, J.M., Weiss, S.J., 2013. Brain regions associated with psychological pain: implications for a neural network and its relationship to physical pain. Brain Imaging Behav. 7 (1), 1–14. https://doi.org/10.1007/s11682-012-9179-y.
Mega, M.S., Cummings, J.L., Salloway, S., Malloy, P., 1997. The limbic system: an anatomic, phylogenetic, and clinical perspective. J. Neuropsychiatry Clin. Neurosci. 9 (3), 315–330.
Meredith, M.A., 2002. On the neuronal basis for multisensory convergence: a brief overview. Brain Res. Cogn. Brain Res. 14 (1), 31–40. https://doi.org/10.1016/s0926-6410(02)00059-9.
Mesulam, M., 2000. Brain, mind, and the evolution of connectivity. Brain Cogn. 42 (1), 4–6. https://doi.org/10.1006/brcg.1999.1145 S0278-2626(99)91145-4 [pii].
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. doi:1471-2202-11-40 [pii] 10.1186/1471-2202-11-40.
Mohan, A., De Ridder, D., Vanneste, S., 2016. Graph theoretical analysis of brain connectivity in phantom sound perception. Sci. Rep. 6, 19683. https://doi.org/10.1038/srep19683.
Mohan, A., Luckey, A., Weisz, N., Vanneste, S., 2022. Predisposition to domain-wide maladaptive changes in predictive coding in auditory phantom perception. Neuroimage 248, 118813. https://doi.org/10.1016/j.neuroimage.2021.118813.
Morrill, R.J., Hasenstaub, A.R., 2018. Visual information present in infragranular layers of mouse auditory cortex. J. Neurosci. 38 (11), 2854–2862. https://doi.org/10.1523/JNEUROSCI.3102-17.2018.
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.
Ohashi, H., Ito, T., 2019. Recalibration of auditory perception of speech due to orofacial somatosensory inputs during speech motor adaptation. J. Neurophysiol. 122 (5), 2076–2084. https://doi.org/10.1152/jn.00028.2019.
Pascual-Marqui, R.D., 2002. Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. Methods Find. Exp. Clin. Pharmacol. 24, 5–12. Suppl D.
Pascual-Marqui, R. (2007a). Discrete, 3D distributed, linear imaging methods of electric neuronal activity. Part 1: exact, zero error localization.
Pascual-Marqui, R. (2007b). Instantaneous and lagged measurements of linear and nonlinear dependence between groups of multivariate time series: frequency decomposition.
Ramachandran, V.S., Rogers-Ramachandran, D., 1996. Synaesthesia in phantom limbs induced with mirrors. Proc. Biol. Sci. 263 (1369), 377–386. https://doi.org/10.1098/rspb.1996.0058.
Riley, J. W. (2017). *Poems & Prose Sketches*: Portable Poetry.
Schirinzi, E., Gandoglia, I., Assini, A., Rikani, K., Siri, G., Pontali, E., Del Settea, M., 2021. Asymptomatic peripheral neuropathy in patients with SARS-CoV-2 infection. J. Neurol. Sci. 429, 95.
Schlee, W., Hartmann, T., Langguth, B., Weisz, N., 2009. Abnormal resting-state cortical coupling in chronic tinnitus. BMC Neurosci. 10, 11. https://doi.org/10.1186/1471-2202-10-11.
Sedley, W., Gander, P.E., Kumar, S., Kovach, C.K., Oya, H., Kawasaki, H., Griffiths, T.D., 2016. Inference. Elife 5, e11476.
Shore, S.E., Zhou, J., 2006. Somatosensory influence on the cochlear nucleus and beyond. Hear. Res. 216–217, 90–99.
Smallwood, R.F., Laird, A.R., Ramage, A.E., Parkinson, A.L., Lewis, J., Clauw, D.J., Robin, D.A., 2013. Structural brain anomalies and chronic pain: a quantitative meta-analysis of gray matter volume. J. Pain 14 (7), 663–675. https://doi.org/10.1016/j.jpain.2013.03.001.
Soleimani, R., Jalali, M.M., Hasandokht, T., 2016. Therapeutic impact of repetitive transcranial magnetic stimulation (rTMS) on tinnitus: a systematic review and meta-analysis. Eur. Arch. Otorhinolaryngol. 273 (7), 1663–1675. https://doi.org/10.1007/s00405-015-3642-5.
Song, J.J., De Ridder, D., Van de Heyning, P., Vanneste, S., 2012a. Mapping tinnitus-related brain activation: an activation-likelihood estimation metaanalysis of PET studies. J. Nucl. Med. jnumed.112.102939 [pii] 10.2967/jnumed.112.102939.
Song, J.J., Vanneste, S., Van de Heyning, P., De Ridder, D., 2012b. Transcranial direct current stimulation in tinnitus patients: a systemic review and meta-analysis. ScientificWorldJournal 2012, 427941. https://doi.org/10.1100/2012/427941.
To, W.T., Ost, J., Hart Jr., J., De Ridder, D., Vanneste, S., 2017. The added value of auditory cortex transcranial random noise stimulation (tRNS) after bifrontal transcranial direct current stimulation (tDCS) for tinnitus. J. Neural Transm. (Vienna) 124 (1), 79–88. https://doi.org/10.1007/s00702-016-1634-2.
Trudeau-Fisette, P., Ito, T., Menard, L., 2019. Auditory and somatosensory interaction in speech perception in children and adults. Front. Hum. Neurosci. 13, 344. https://doi.org/10.3389/fnhum.2019.00344.
Van den Bergh, O., Brosschot, J., Critchley, H.D., Thayer, J.F., Ottaviani, F., 2021. Better safe than sorry: a common signature of general vulnerability for psychopathology. Perspect. Psychol. Sci. 16 (2), 225–246.
van der Loo, E., Congedo, M., Vanneste, S., De Heyning, P.V., De Ridder, D., 2011. Insular lateralization in tinnitus distress. Auton. Neurosci. 165 (2), 191–194. S1566-0702(11)00384-5 [pii] 10.1016/j.autneu.2011.06.007.
Vanneste, S., De Ridder, D., 2012. The auditory and non-auditory brain areas involved in tinnitus. an emergent property of multiple parallel overlapping subnetworks. Front. Syst. Neurosci. 6, 31. https://doi.org/10.3389/fnsys.2012.00031.
Vanneste, S., De Ridder, D., 2013. Brain areas controlling heart rate variability in tinnitus and tinnitus-related distress. PLoS One 8 (3), e59728.
Vanneste, S., De Ridder, D., 2016. Deafferentation-based pathophysiological differences in phantom sound: tinnitus with and without hearing loss. Neuroimage 129, 80–94. https://doi.org/10.1016/j.neuroimage.2015.12.002.
Vanneste, S., De Ridder, D., 2021. Chronic pain as a brain imbalance between pain input and pain suppression. Brain Commun 3 (1), fcab014. https://doi.org/10.1093/braincomms/fcab014.
Vanneste, S., Plazier, M., der Loo, E., de Heyning, P.V., Congedo, M., De Ridder, D., 2010. The neural correlates of tinnitus-related distress. Neuroimage 52 (2), 470–480. S1053-8119(10)00441-6 [pii] 10.1016/j.neuroimage.2010.04.029.
Vanneste, S., Fregni, F., De Ridder, D., 2013a. Head-to-head comparison of transcranial random noise stimulation, transcranial AC stimulation, and transcranial DC stimulation for tinnitus. Front. Psych. 4, 158. https://doi.org/10.3389/fpsyt.2013.00158.
Vanneste, S., Walsh, V., Van De Heyning, P., De Ridder, D., 2013b. Comparing immediate transient tinnitus suppression using tACS and tDCS: a placebo-controlled study. Exp. Brain Res. 226 (1), 25–31. https://doi.org/10.1007/s00221-013-3406-7.
Wang, J., Fan, J., Gc, R., Zhao, J., 2022. Comparative effects of interventions on phantom limb pain: a network meta-analysis. World Neurosurg. https://doi.org/10.1016/j.wneu.2022.10.060.
Wang, T.C., Tyler, R.S., Chang, T.Y., Chen, J.C., Lin, C.D., Chung, H.K., Tsou, Y.A., 2018. Effect of transcranial direct current stimulation in patients with tinnitus: a meta-analysis and systematic review. Ann. Otol. Rhinol. Laryngol. 127 (2), 79–88. https://doi.org/10.1177/0003489417744317.
Weisz, N., Hartmann, T., Dohrmann, K., Schlee, W., Norena, A., 2006. High-frequency tinnitus without hearing loss does not mean absence of deafferentation. Hear. Res. 222 (1–2), 108–114. S0378-5955(06)00252-8 [pii] 10.1016/j.heares.2006.09.003.
Wu, C., Stefanescu, R.A., Martel, D.T., Shore, S.E., 2015. Listening to another sense: somatosensory integration in the auditory system. Cell Tissue Res. 361 (1), 233–250. https://doi.org/10.1007/s00441-014-2074-7.
Xie, H.M., Zhang, K.X., Wang, S., Wang, N., Wang, N., Li, X., Huang, L.P., 2022. Effectiveness of mirror therapy for phantom limb pain: a systematic review and meta-analysis. Arch. Phys. Med. Rehabil. 103 (5), 988–997. https://doi.org/10.1016/j.apmr.2021.07.810.

Further reading

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.
Siepmann, M., Kirch, W., 2002. Effects of caffeine on topographic quantitative EEG. Neuropsychobiology 45 (3), 161–166.
Volkow, N.D., Logan, J., Fowler, J.S., Wang, G.J., Gur, R.C., Wong, C., 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.