Invariant structural and functional brain regions associated with tinnitus: A meta-analysis

John C. Moring, Fatima T. Husain, Jodie Gray, Crystal Franklin, Alan L. Peterson, Patricia A. Resick, Amy Garrett, Carlos Esquivel, Peter T. Fox

1 Department of Psychiatry and Behavioral Sciences, University of Texas Health Science Center at San Antonio, San Antonio, Texas, United States of America, 2 Department of Speech and Hearing Science and the Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign, Champaign, Illinois, United States of America, 3 Research and Development Service, South Texas Veterans Health Care System, San Antonio, Texas, United States of America, 4 University of Texas at San Antonio, San Antonio, Texas, United States of America, 5 Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina, United States of America, 6 Hearing Center of Excellence, Wilford Hall Ambulatory Surgical Center, San Antonio, Texas, United States of America

☯ These authors contributed equally to this work.
‡ These authors also contributed equally to this work.
* MoringJ@uthscsa.edu

Abstract

Tinnitus is a common, functionally disabling condition of often unknown etiology. Neuroimaging research to better understand tinnitus is emerging but remains limited in scope. Voxel-based physiology (VBP) studies detect tinnitus-associated pathophysiology by group-wise contrast (tinnitus vs controls) of resting-state indices of hemodynamics, metabolism, and neurovascular coupling. Voxel-based morphometry (VBM) detects tinnitus-associated neurodegeneration by group-wise contrast of structural MRI. Both VBP and VBM studies routinely report results as atlas-referenced coordinates, suitable for coordinate-based meta-analysis (CBMA). Here, 17 resting-state VBP and 8 VBM reports of tinnitus-associated regional alterations were meta-analyzed using activation likelihood estimation (ALE). Acknowledging the need for data-driven insights, ALEs were performed at two levels of statistical rigor: corrected for multiple comparisons and uncorrected. The corrected ALE applied cluster-level inference thresholding by intensity (z-score > 1.96; p < 0.05) followed by family-wise error correction for multiple comparisons (p < .05, 1000 permutations) and fail-safe correction for missing data. The corrected analysis identified one significant cluster comprising five foci in the posterior cingulate gyrus and precuneus, that is, not within the primary or secondary auditory cortices. The uncorrected ALE identified additional regions within auditory and cognitive processing networks. Taken together, tinnitus is likely a dysfunction of regions spanning multiple canonical networks that may serve to increase individuals’ interoceptive awareness of the tinnitus sound, decrease capacity to switch cognitive sets, and prevent behavioral and cognitive attention to other stimuli. It is noteworthy that the most robust tinnitus-related abnormalities are not in the auditory system, contradicting collective findings of task-activation literature in tinnitus.
Introduction

Subjective tinnitus is the perception of sound in the absence of any external sound source (i.e., an illusory percept). Tinnitus is commonly described as ringing, buzzing, whooshing, or a combination of sounds in one or both ears [1,2]. Tinnitus prevalence varies from 3%-14% in the general population [3]. Roughly 1–3% of individuals with tinnitus report significant functional impairment [4,5], including difficulties with sleeping, concentration, and communication. Combinations of tinnitus sounds (e.g., ringing and buzzing or buzzing and whooshing) cause significantly more impairment than a single percept [6]. Although tinnitus is a common, functionally disabling condition that has been described in the medical literature for millennia [7,8], the neurobiology of tinnitus remains unsolved. Over roughly the past two decades, a modest body of neuroimaging studies has emerged seeking to address this shortcoming.

Neuroimaging studies fall into two broad classes: functional and structural. In both classes, atlas-referenced coordinates are widely used, making the literatures amenable to coordinate-based meta-analysis (CBMA; [9–11]). Functional studies can be further subdivided into task-activation (TA) and resting-state (RS). The early neuroimaging literature in most disorders, including tinnitus, relied heavily on TA methodology. A distinct advantage of the task-activation approach is the high signal-to-noise ratio of the task-induced activations and, secondarily, of the superimposed inter-group, condition-related differences in activation. The TA literature was, from the outset, reliant on coordinate-based reporting. The cardinal limitations of the TA approach are: (1) regions probed are largely limited to those engaged by the task; (2) sensitivity is reliant on participant performance, which can be highly variable in clinical populations; and (3) there are a wide range of control tasks that are employed. The majority of the tinnitus TA literature has used sound stimuli as a probe, and this was meta-analyzed by Song and colleagues [12]. Tinnitus-related increases in activation were observed but, predictably, these increases were almost entirely limited to primary and secondary auditory cortices.

Between-group contrasts (disease vs control) of resting-state physiology using PET and SPECT have been reported in tinnitus since the late 1990s [13,14], prior to the widespread adoption of statistical parametric mapping using standardized coordinates for non-task studies in clinical cohorts. Reviews of this early literature were conducted by Adjamian [15] and Lanting [16]. More recently, resting-state fMRI (rs-fMRI) measures have been ascendant, exploiting both hemodynamic measures (e.g., arterial spin labeling; ASL) and BOLD-derived metrics of neurovascular coupling, most notably regional homogeneity (ReHo; [17]) and fractional amplitude of low-frequency fluctuations (fALFF; [18]). Here we refer to resting-state fMRI, PET, FDR-PET, and SPECT studies which apply mass-univariate statistics (the same operation is performed on each image voxel) and report in standardized coordinates as voxel-based physiology (VBP) studies. By reporting standardized coordinates, the VBP literature provides suitable input for CBMA. By assessing participants in the resting-state, this literature provides a regionally unbiased examination of the gray-matter physiology in persons with tinnitus, which is a distinct paradigm shift from the task-activation literature. Resting-state VBP studies using fMRI (60%; 15/25) form the bulk of the literature meta-analyzed here.

Resting-state contrasts of brain structure, also task independent, most often are performed using voxel-based morphometry (VBM; [19]) applied to T1-weighted MRI. VBM, like VBP, is a mass-univariate method in which spatially standardized images are contrasted group-wise to detect abnormalities too subtle to be recognized by visual inspection, but which are sufficiently reliable in location to be detected by group-wise contrasts. Like VBP studies, VBMs are regionally unbiased with the caveat that VBM—like VBP—are most sensitive for detecting gray-matter effects. VBM gray-matter studies make up the remainder (32%; 8/25) of the literature examined herein.
Activation/anatomical likelihood estimation (ALE: [9,20,21]) is the most widely utilized CBMA algorithm [22]. Although ALE CBMA was originally designed for task-activation meta-analysis and has been most extensively used for single-modality, (see BrainMap.org/pubs), this is not an intrinsic limitation of the ALE method. Rather, ALE assesses the spatial proximity of reported coordinates against a null hypothesis of a random distribution of the same volume and quality of data. ALE computes the convergence of findings based solely on location and is blind to magnitude and direction [23]. Therefore, this modality agnosticism allows ALE the flexibility to integrate findings across imaging methods [24,25], if to do so is logically appropriate. Co-localization of structural and functional alterations are found in numerous neurodegenerative and psychiatric disorders [25]. Since studies have found both structural and functional alterations related to tinnitus, it is appropriate to implement the ALE algorithm. Results will identify the disease effects related to gray matter alterations and the co-localization of both increases and decreases in resting-state function. In the present study, we combined resting-state VBP studies and VBM studies contrasting persons with tinnitus to healthy controls for a comprehensive assessment of tinnitus-related gray-matter alterations. Significant group contrasts, between tinnitus groups and control groups from each study were included in the meta-analysis, independent of whether results indicated increased/decreased GM/resting-state function. According to Müller et al. [26], multiple experiments with the same set of participants can compromise the validity of results. Therefore, the procedures of this meta-analysis included only one experiment per subject group.

Acknowledging the limited volume of the quantitative, coordinate-reporting literature in tinnitus and the necessity for data-driven etiological insights, CBMAs were performed at two levels of statistical rigor: confirmatory and exploratory. The more conservative approach applied two statistical thresholds: (1) intensity ($p < 0.05$) at the voxel level; and, (2) a correction for multiple comparisons at the cluster-forming level using family-wise error rate (FWE; 1,000 permutations, $p < 0.05$). Additionally, the fail-safe correction for missing data (publication bias) was applied [22,25]. The less conservative approach applied only voxel-wise thresholds, with no corrections for multiple comparisons or missing data. The intent of this exploratory analysis was to probe the available data as deeply as possible and thereby simulate hypothesis generation as well as to identify candidate nodes for network analyses.

The overall goal of the present study was to identify brain regions exhibiting tinnitus-related functional and structural alterations in the absence of task performance by applying CBMA to the VBP and VBP literatures. The null hypothesis of ALE CBMA is spatial non-convergence (i.e. a random data distribution). The hypothesis of the investigators was that this task-free approach would demonstrate abnormalities outside the confines of the auditory system and provide new, data-driven insights into the pathophysiology of tinnitus [27–29].

Methods

Literature search

A literature search of PubMed, BrainMap [10,21,30–34], Scopus, and Science Direct was performed to identify tinnitus VBM and VBP studies, comparing individuals with tinnitus to healthy controls. Trace referencing was also conducted to identify studies with the same criteria. Included studies of gray-matter volume utilized VBM methods. Studies of resting-state VBP included glucose metabolism, amplitude of low frequency fluctuations (ALFF/fALFF), regional homogeneity (ReHo), and regional cerebral blood flow (rCBF). Search terms included: tinnitus; resting-state; brain activity; arterial spin labeling OR ASL; regional homogeneity OR ReHo; glucose metabolism; single photon emission computed tomography OR SPECT; positron emission tomography OR PET; regional cerebral blood flow OR rCBF; gray
matter; voxel-based morphometry OR VBM. Any studies that were ambiguous regarding meeting inclusion criteria were screened by a second author. The literature search was completed January 2020. A study selection diagram for this meta-analysis can be seen in Fig 1.

**Study selection criteria pertaining to indices of quality**

Selection criteria required that studies be peer-reviewed, English language neuroimaging reports, included application of motion correction, and included participants with unilateral, bilateral, subjective, or pulsatile tinnitus, with any degree of hearing loss. Studies must have compared tinnitus groups to control groups that consisted of participants without any type of tinnitus and must have used voxel-wise whole-brain methods. Studies must have reported results as coordinates using standard reference space: Talairach or Montreal Neurological Institute (MNI). Studies that did not report results in the form of standardized coordinates were excluded from analyses. Data collation was conducted by the first author. The data that support the findings are available in Open Science Framework [35].

**Corrected ALE**

The dual threshold CBMA ALE was conducted with cluster-level threshold and family-wise error rate of \( p < .05 \), 1000 thresholding permutations, and intensity threshold of \( p < .05 \). The intensity threshold was chosen based on the recommendations for conducting neuroimaging meta-analyses [26]. The cluster-level FWE threshold of \( p < .001 \) resulted in no effects, and therefore, the cluster-level threshold FWE threshold was expanded to \( p < .05 \). ALE examines the spatial convergence among previously reported coordinates of the included
tinnitus studies and tests the null hypothesis that coordinates are randomly distributed rather than statistically convergent. This approach is blind to magnitude and sign (+/-) and computes the convergence of findings based solely on location. This flexibility allows for ALE to incorporate findings from across imaging modalities [25] to determine the most statistically convergent brain regions related to the disease effects of tinnitus. ALE was computed using GingerALE, [21,30,31] version 3.0 (http://brainmap.org) which simulates random coordinates based on study sizes to simulate noise and increase robustness of results [36].

**Noise simulation.** The current ALE algorithm does not take into account publication biases, in which only significant findings are published, otherwise known as the file drawer effect. Fortunately, Acar et al. [22] developed the fail-safe N method in order to account for publication bias by introducing noise into the ALE algorithm. A modified version of the fail-safe N method [25] was implemented, which introduced 6% noise. Increased noise was introduced until results were no longer significant.

**Uncorrected ALE**

Additionally, we implemented a less conservative approach to identify other possible relevant regions impacted by disease effects of tinnitus. This approach did not use statistical methods to correct for multiple comparisons. Thresholds of intensity (\(p < .01\)) and extent (minimum volume set at 450mm\(^3\)) were implemented for exploratory purposes. A stricter threshold, compared to the dual-threshold method, was used because the recommended threshold of \(p < .05\) resulted in over 120 regions, which is not interpretable or meaningful. The more conservative approach that was used also simultaneously limits potential for Type 1 error.

**Results**

A total of 25 studies (26 experiments), with 791 participants with tinnitus, were identified for inclusion in this meta-analysis (Table 1). Fig 1 shows the flow diagram of study selection. The all-effects analysis comprised a total of 148 foci from all experiment types. The FWE corrected ALE demonstrated one cluster with five regions of convergence (Fig 2): cingulate gyrus, precuneus, and three regions within the posterior cingulate gyrus (PCG)/precuneus, with a minimum cluster size of 5,728 mm\(^3\). Coordinates and peak ALE scores from the dual-threshold ALE can be seen in Table 2.

The fail-safe N method assessed the robustness of the corrected ALE findings, which accounted for unpublished findings. A total of 6% noise was added to the meta-analysis, and results remained consistent regarding the significant cluster and five regions of convergence described above. However, when 11% of added noise was added to the meta-analytic data, these results were not replicated.

After implementation of an uncorrected ALE, results demonstrated 15 regions across 10 clusters. The first cluster contained the inferior parietal lobe and insula, while the second cluster replicated the findings from the corrected ALE. This particular cluster contained one region: the cingulate gyrus. Additional regions within the remaining nine clusters included the middle temporal gyrus, lingual gyrus, middle occipital gyrus, cuneus, medial frontal gyrus, subcallosal gyrus, and thalamus. Fig 3 shows the clusters that resulted from the single-threshold ALE. Coordinates and peak ALE scores from the single-threshold ALE can be seen in Table 3. The data that support all findings are available in Open Science Framework at osf.io [35].
Table 1. Studies included in meta-analysis.

| Study | Journal | Modality | Patient N | Control N | Mean Age Patient | Mean Age Control | Foci No. | Scanner Processing Software | Smoothing kernel (mm) | Statistical threshold | MNI or Tal |
|-------|---------|----------|-----------|-----------|------------------|------------------|----------|----------------------------|----------------------|----------------------|-----------|
| [37] Boyen et al. (2013) | Hearing Research | VBM | 31 | 24 | 56 | 58 | 9 | Philips 3T | SPM5 | .05 FWE | MNI |
| [38] Carpenter-Thompson et al. (2014) | Brain Research | BOLD | 13 | 24 | 54.7 | 51.4 | 20 | Siemens 3T | SPM8 | .05 FWE | MNI |
| [39] Chen et al. (2014) | Neuroimage: Clinical | BOLD-ALFF | 31 | 32 | 41.9 | 46.5 | 7 | Siemens 3T | SPM8 | .05 AlphaSim | MNI |
| [40] Chen et al. (2015) | Neural Plasticity | BOLD-Reho | 29 | 30 | 40.9 | 46.2 | 5 | Siemens 3T | SPM8 | .01 AlphaSim | MNI |
| [41] Chen et al. (2016) | Frontiers in Aging Neuroscience | BOLD-DC | 24 | 22 | 50.8 | 44.7 | 5 | Philips 3T | SPM8 | .01 AlphaSim | MNI |
| [42] Gentil et al. (2019) | Trends in Hearing | BOLD-Reho | 19 | 16 | 63 | 59 | 1 | Siemens 3T | SPM12 | .005 | MNI |
| [43] Geven et al. (2014) | Neuroscience | FDG-PET | 20 | 19 | 51 | 50.8 | 2 | Siemens | SPM5 | .001 Uncorrected | MNI |
| [44] L. Han et al. (2015) | Neuroscience | FCD | 32 | 32 | 37.1 | 38.5 | 16 | GE 3T | SPM8 | .05 AlphaSim | MNI |
| [45] Lv Han et al. (2015) | Progress in Neuro-Psychopharmacology and Biological Psychiatry | BOLD-ReHo/ALFF | 34 | 34 | 37.9 | 39.5 | 14 | GE 3T | SPM8 | .05 Monte Carlo | MNI |
| [46] Han et al. (2014) | Neural Plasticity | BOLD-ALFF | 42 | 42 | 37.2 | 37 | 11 | GE 3T | SPM8 | .01 Monte Carlo | MNI |
| [47] Han et al. (2018) | Neuroradiology | BOLD-ReHo | 25 | 25 | 44.7 | 44 | 5 | Siemens 3T | SPM8 | .05 AlphaSim | MNI |
| [27] Hussain et al. (2011) | Brain Research | VBM | 8 | 18 | 56.1 | 51.4 | 5 | GE 3T | SPM5 | .001 Uncorrected | MNI |
| [48] Laureano et al. (2014) | PloS One | SPECT | 20 | 17 | 42.9 | 41.4 | 1 | GE | SPM8 | .05 FWE | MNI |
| [49] Leaver et al. (2012) | Frontiers in Systems Neuroscience | VBM | 23 | 21 | 47.4 | 49 | 3 | Siemens 3T | SPM8 | .05 Uncorrected | MNI |
| [50] Leaver et al. (2016) | Human Brain Mapping | BOLD-ICA | 21 | 19 | 47.3 | 48.9 | 5 | Siemens 3T | Brain Voyager | .0005 Uncorrected | Tal |
| [51] Liu et al. (2018) | Neural Plasticity | VBM | 24 | 24 | 34.9 | 35.3 | 7 | GE 3T | SPM8 | .001 Uncorrected | MNI |
| [52] Ly et al. (2017) | Hearing Research | BOLD-ReHo | 45 | 45 | 37.3 | 37.2 | 4 | GE 3T | SPM8 | .01 FDR | MNI |
| [53] Maudoux et al. (2012) | PloS One | BOLD-ICA | 13 | 15 | 52 | 51 | 17 | Siemens 3T | Brain Voyager | .05 FDR | Tal |
| [54] Melcher et al. (2013) | Hearing Research | VBM | 24 | 24 | 46.9 | 45.8 | 1 | Siemens 3T | SPM8 | .001 Uncorrected | MNI |
| [55] Mühlaus et al. (2006) | Cerebral Cortex | VBM | 28 | 28 | 40 | 39 | 1 | Siemens 1.5T | SPM2 | .05 FDR | MNI |
| [56] Schmidt et al. (2018) | Brain Research | VBM | 15 | 13 | 13 | 15 | 55.1 | Siemens 3T | SPM12 | .05 FWE | MNI |

(Continued)
Discussion

Summary

The current findings represent the disease effects of tinnitus in grey matter, glucose metabolism, and blood flow. Two ALEs were implemented with different levels of statistical rigor: corrected for multiple comparisons and uncorrected. The cluster-level inference ALE with family-wise error (FWE) rate was more stringent and demonstrated one cluster with five regions related to the disease effects of tinnitus. These regions included the posterior cingulate gyrus/precuneus and cingulate gyrus. Moreover, these regions remained significant in relation to tinnitus disease-effects after introducing 6% added noise, which accounts for negative

Table 1. (Continued)

| Study | Journal | Modality | Patient N | Control N | Mean Age Patient | Mean Age Control | Foci No. | Scanner | Processing Software | Smoothing kernel (mm) | Statistical threshold | MNI or Tal |
|-------|---------|----------|-----------|-----------|------------------|------------------|----------|---------|---------------------|----------------------|---------------------|-----------|
| [57] Seydell-Greenwald et al. (2012) | Brain Research | BOLD | 20 | 20 | 47 | 49 | 2 | Siemens 3T | Brain Voyager | 6 | .005 | Uncorrected | Tal |
| [58] Vanneste et al., (2015) | PLoS One | VBM | 154 | - | 50.24 | NA | 9 | Siemens 3T | SPM8 | 8 | .001 | Uncorrected | MNI |
| [59] Yang et al. (2014) | Journal of Otology | BOLD-ReHo | 18 | 20 | 43 | 42 | 2 | Philips 3T | SPM5 | NA | .05 FWE | MNI |
| [60] Zhou et al. (2019) | Frontiers in Neuroscience | BOLD-ReHo/FALFF | 28 | 31 | 41.2 | 45.4 | 6 | Philips 3T | SPM8 | 4 | .001 | AlphaSim | MNI |

Fig 2. Regions identified by corrected ALE. Note: 1 = Cingulate Gyrus; 2 = Precuneus; 3 = Cingulate Gyrus/Precuneus; 4 = Posterior Cingulate/Precuneus; 5 = Posterior Cingulate/Precuneus.

https://doi.org/10.1371/journal.pone.0276140.g002
unpublished findings. The second approach did not implement a statistical correction for multiple comparisons, which was less stringent, and identified 15 additional regions across 10 clusters. These regions included the cingulate gyrus, occipital temporal gyrus, lingual gyrus, middle occipital gyrus, cuneus, medial frontal gyrus, subcallosal gyrus, and thalamus.

Findings from the cluster-level inference ALE with FWE serve as an out-of-sample replication of previous tinnitus neuroimaging studies of resting-state functional connectivity. Resting-state functional connectivity measures temporal correlations of spontaneous BOLD signals across brain regions [61] to identify disease-related networks. For example, Schmidt et al. [62] found that individuals with tinnitus exhibited decreased connectivity within the left precuneus, left precentral gyrus, and left cerebellum, compared to individuals with hearing loss and no tinnitus. Additional out-of-sample replications are observed by the findings from the ALE without FWE regarding the auditory dorsal attention network (DAN).

Our results demonstrate consistent disease-related effects of tinnitus across a heterogeneous population that varies in tinnitus sounds, loudness, laterality, and duration of tinnitus. Other medical and psychological comorbidities, such as head injury, hearing loss, depression, post-traumatic stress disorder, and anxiety, were not controlled in the current study; nor were the data acquisition techniques and data analytic approaches. Therefore, it is suggested that the identified regions from this meta-analysis, particularly from the cluster-level inference ALE with FWE, are invariant and shared across the spectrum of tinnitus patients. Findings are explained in the context of the resting-state network [28,63] for which specific regions are most identified with.

### Corrected ALE

**Default mode network.** The cluster-level inference ALE with FWE demonstrated the disease-effects of tinnitus occur within the posterior cingulate cortex (PCC), cingulate gyrus, and precuneus, which play a central role within the default mode network [64–68]. It is important to note that the studies that contributed to the significant clusters found by the ALE indicated heightened activation for those with tinnitus, when compared to controls [38,44–46,52,60]. Interestingly, there were no VBM studies that contributed to these results. The default mode network (DMN) is a “task negative network” [32], meaning that it is more highly activated at “rest;” however, recent research suggests a more complicated pattern, specifically within the PCC [69]. In addition to task-free states, the PCC is likely involved in ongoing experiences, most notably self-generated thoughts such as daydreaming, the recollection of autobiographical information, and future planning, particularly of a social nature [64,70]. A recent meta-analytic study demonstrated the significant role of the PCC in domains of cognition, and particularly in attention, language, and memory [71]. Moreover, the same study differentiated

### Table 2. Identified regions from corrected ALE.

| Region Name                  | MNI Coordinate (x, y, z) | BA  | Peak ALE Score | Peak Z Score | Fail-Safe N (%) |
|------------------------------|--------------------------|-----|----------------|--------------|-----------------|
| Cingulate Gyrus              | 2, -42, 32               | 31  | .022           | 5.043        | 11% > FSN > 6%  |
| Precuneus                    | -6, -54, 42              | 7   | .010           | 3.090        | 11% > FSN > 6%  |
| Cingulate Gyrus/Precuneus    | -6, -54, 30              | 31  | .009           | 3.023        | 11% > FSN > 6%  |
| Posterior Cingulate/Precuneus| 0, -58, 22               | 23  | .009           | 2.890        | 11% > FSN > 6%  |
| Posterior Cingulate/Precuneus| 8, -60, 28               | 31  | .008           | 2.507        | 11% > FSN > 6%  |

Note: ALE = Activation Likelihood Estimate; BA = Brodmann Area; MNI = Montreal Neurological Institute.

https://doi.org/10.1371/journal.pone.0276140.t002
between the dorsal and ventral PCC (dPCC and vPCC, respectively) and found that the dPCC was highly co-activated with regions associated with consciousness and awareness of internal bodily sensations, hereafter called interoceptive awareness. Additionally, the vPCC was found to co-activate with regions associated with self-awareness. Related to tinnitus and the results of the current study, alteration of the PCC may hinder tinnitus patients from appropriately directing their attention away from irrelevant noise sources, and instead, increase individuals’ attention and awareness to the tinnitus percept. Therefore, therapies should aim to provide...
individuals with tinnitus the techniques to increase their capability of re-directing their focus from their tinnitus and instead to the present moment and engaging in value-based activities, such as mindfulness-based cognitive therapy [72]. Future psychotherapies and neuromodulatory approaches should aim to decrease the activation within the DMN; however, additional research is warranted concerning the connectomic properties of the DMN among tinnitus patients.

It is important to note that the cluster-level inference CBMA ALE with FWE did not detect any regions within the auditory RSN. Instead, the superior, middle, and inferior temporal gyrus was detected by the single-threshold CBMA ALE, discussed later. Past and current perspectives on tinnitus have heavily relied on the assumption that auditory regions are most implicated for the genesis and maintenance of tinnitus. While it is certainly understandable to conceptualize tinnitus as an auditory disorder, a detriment of this approach includes a hyper-focus on the auditory RSN, and therefore, a concurrent and serious neglect of other significant regions and networks.

Our results offer strong support for the paradigm shift in the field of tinnitus regarding the specific neurobiological disease-related effects of the disorder [64,73]. It is especially noteworthy that the regions within the DMN, found to be significantly associated with tinnitus, survived a fail-safe N correction for unreported negative finding, adding up to 6% random noise. Therefore, even when accounting for unpublished results, the corrected ALE demonstrates results with an acceptable amount of added noise [74]. Extant research, however, is heavily influenced by the notion that tinnitus is an auditory disorder; and therefore, significant differences in brain structure and function should be found within the auditory network (AUD). Song et al. [12] conducted a TA tinnitus meta-analysis among 10 studies, in which 6 of the studies did not have a control group, and two of the remaining studies used sound as the task dimension. Beyond the criticism related to insufficient studies to perform CBMA ALE [26],

| Region Name                    | MNI Coordinate (x, y, z) | BA  | Peak ALE Score | Peak Z Score |
|--------------------------------|--------------------------|-----|----------------|--------------|
| R Inferior Parietal Lobule     | 64, -30, 24              | 40  | .018           | 4.459        |
| R Insula                       | 56, -28, 22              | 13  | .010           | 3.062        |
| R Superior Temporal Gyrus      | 60, -40, 24              | 13  | .009           | 2.831        |
| L Cingulate Gyrus              | 2, -42, 32               | 31  | .022           | 5.043        |
| R Middle Temporal Gyrus        | 58, -54, -8              | 37  | .013           | 3.577        |
| R Middle Temporal Gyrus        | 54, -56, 0               | 37  | .009           | 3.002        |
| L Lingual Gyrus                | -2, -94, 2               | 18  | .015           | 4.005        |
| R Inferior Parietal Lobule     | 42, -42, 42              | 40  | .010           | 3.126        |
| R Precuneus                    | 34, -40, 42              | 7   | .009           | 3.008        |
| R Inferior Parietal Lobule     | 46, -48, 44              | 40  | .008           | 2.604        |
| L Middle Occipital Gyrus       | -26, -96, 10             | 18  | .018           | 4.459        |
| L Cuneus                       | -14, -88, 16             | 17  | .013           | 3.632        |
| R Middle Frontal Gyrus         | 4, 4, 54                 | 6   | .013           | 3.655        |
| R Subcallosal Gyrus            | 22, 18, -22              | 47  | .010           | 3.154        |
| R Thalamus                     | 10, 14, -10              | -   | .010           | 3.148        |

Note: ALE = Activation Likelihood Estimate; BA = Brodmann Area; L = Left; MNI = Montreal Neurological Institute; R = Right.

https://doi.org/10.1371/journal.pone.0276140.t003
this study is overly reliant on sound tasks that undoubtedly increases potential for Type I error, specifically related to the auditory network. Moreover, the field has neglected findings that have demonstrated significant effects of tinnitus, beyond the AUD. One glaring example of this neglect in tinnitus neuroimaging research is found in Farhadi et al. [75], in which authors focus on results solely related to temporal regions despite the clear implication of the cingulate gyrus. In order to progress the field of tinnitus research, investigators must recognize the effects of regions across canonical networks, and rely less heavily on past assumptions.

**Uncorrected ALE**

In addition to the rigorous meta-analysis discussed above, an uncorrected meta-analysis was conducted to detect all possible alterations that might represent disease-effects of tinnitus. This less conservative approach has a greater probability of Type I error; however, due to the relative novelty of tinnitus neuroimaging research, it is important to identify a larger set of regions that may otherwise be overlooked. In this sense, future research can determine whether these regions are significantly associated with tinnitus. The regions identified beyond what was found by the ALE can be discussed in relation to two RSNs: auditory (AUD) and cognitive processes.

**Auditory.** Disease-effects of tinnitus within the AUD were discovered when the uncorrected ALE was implemented. Specifically, the middle temporal gyrus and sub-gyral (non-cortical) regions within AUD demonstrated alterations. The middle temporal gyrus (MTG) is an extra-primary cortical component of the auditory network strongly implicated in language and of semantic processing, in particular [76,77]. Individuals experiencing hearing loss with and without tinnitus demonstrate increased gray matter in the MTG when compared to individuals without tinnitus or hearing loss [37]. Therefore, the MTG may be more related to hearing loss, rather than tinnitus. However, alterations within the right MTG have also been demonstrated among tinnitus sufferers both as structural differences and in spontaneous neural activity [78]. Dysregulation within the MTG may be a source of the tinnitus percept, while other regions of the brain may play a role in the loudness and emotional responses associated with tinnitus [79]. Investigation of the functional and structural connectivity between the MTG and other significant regions identified by the current study will likely shed light on specific neurobiological causes of tinnitus and related distress.

**Cognitive processes.** The IPL is a hub of the dorsal attention network (DAN), which is associated with cognitive abilities and top-down processing [80]. Previous research supports the role of the DAN in tinnitus [62,81], and, more recently, increased connectivity between the DAN and precuneus (DMN) has been shown to reflect tinnitus duration and severity [82]. Authors of these studies suggest that the DAN and DMN may not be appropriately suppressed at rest or during tasks, respectively. The DAN may be active “at-rest” and while “task-positive,” representing lack of control away from tinnitus sensation, and perhaps, negative attributions toward tinnitus, even while external noises mask the tinnitus percept. The medial frontal gyrus (MFG) was also found to be a significant brain region based. The MFG (BA 10) is a region associated with executive functioning, which includes motor planning, decision-making, abilities to hold ideas in working memory, as well as switching cognitive sets [83]. Studies have demonstrated decreased grey matter volume within the MFG among individuals with schizophrenia [84], who often have significant deficits in executive functioning tasks. For those with tinnitus, and in relation to the results that implicate the IPL, individuals may have difficulty switching their attention away from tinnitus sounds. As causation cannot be determined, it is also possible that the alterations of the MFG may be due to distractibility related to tinnitus.

**Neural plasticity.** Often referred to as a plasticity disorder [85–87], tinnitus may occur due to compensatory processes, involving deafferentation and increased spontaneous firing of
neurons beyond the auditory pathway [88], causing alterations observed in this meta-analysis. It is suggested that in response to acoustic trauma, individuals who develop tinnitus experience significantly greater structural and functional changes within the posterior cingulate and precuneus, compared to individuals who may have experienced similar acoustic events and did not develop tinnitus. Such changes may also reflect neuroplasticity occurring after onset of chronic tinnitus as individuals adapt to the condition. Longitudinal epidemiologic studies that implement neuroimaging techniques may be able to ascertain the chronological order of changes within these brain regions that can predict development of tinnitus. However, since imaging is conducted during a discrete timeframe, observed neurobiological differences may be a function of events prior to the onset of tinnitus, or the habituation to chronic tinnitus.

**Future directions**

Future studies should aim to more fully characterize, structurally and functionally, altered brain regions indicative of disease-related effects of tinnitus, without the reliance on past assumptions related to the auditory network. These results provide compelling evidence that a paradigm shift is necessary in the field of tinnitus neuroimaging research. Investigators must recognize the effects from specific regions across canonical networks beyond the auditory resting-state network.

Functional modeling may help distinguish the relationship among the regions identified in this meta-analysis, including direct and indirect pathways involved in tinnitus generation, persistence, tolerance, bothersomeness, and habituation. Co-authors of this study aim to identify the functional pathways of tinnitus. By doing so, neuromodulatory therapies may become more refined and tailored to individuals' needs regarding comorbid diagnoses and current health conditions.

**Caveats**

It is feasible that improvement of the spatial resolution of existing tools may lead to the identification of additional altered regions associated with tinnitus. Additionally, this meta-analysis did not control for demographic variables, psychological comorbidities, head injury, hearing loss, or differences in tinnitus percept or related distress. Future neuroimaging studies may account for these differences to map tinnitus in relation to specific comorbidities. Moreover, although ALE found significant regions within clusters, precise areas (e.g., dorsal/ventral PCC) are less well identified.

**Supporting information**

S1 Checklist. PRISMA 2020 checklist.

(DOCX)

**Author Contributions**

**Conceptualization:** John C. Moring, Fatima T. Husain, Alan L. Peterson, Patricia A. Resick, Peter T. Fox.

**Data curation:** Jodie Gray, Crystal Franklin, Peter T. Fox.

**Formal analysis:** John C. Moring, Jodie Gray, Crystal Franklin, Peter T. Fox.

**Funding acquisition:** John C. Moring, Peter T. Fox.

**Investigation:** John C. Moring, Fatima T. Husain, Jodie Gray, Crystal Franklin, Peter T. Fox.
Methodology: John C. Moring, Fatima T. Husain, Jodie Gray, Alan L. Peterson, Amy Garrett, Peter T. Fox.

Project administration: Fatima T. Husain, Crystal Franklin, Peter T. Fox.

Resources: Peter T. Fox.

Supervision: Crystal Franklin, Amy Garrett, Peter T. Fox.

Visualization: Fatima T. Husain, Peter T. Fox.

Writing – original draft: John C. Moring, Fatima T. Husain, Alan L. Peterson, Patricia A. Resick, Amy Garrett, Carlos Esquivel, Peter T. Fox.

Writing – review & editing: John C. Moring, Fatima T. Husain, Jodie Gray, Alan L. Peterson, Patricia A. Resick, Amy Garrett, Carlos Esquivel, Peter T. Fox.

References

1. Andersson G., Bakhsh R., Johansson L., Kaldo V., & Carlbring P. (2005). Stroop facilitation in tinnitus patients: an experiment conducted via the world wide web. Cyberpsychology & Behavior, 8(1), 32–38. https://doi.org/10.1080/cpb.2005.8.32

2. Moring J., Bowen A., Thomas J., & Bira L. (2016). The Emotional and Functional Impact of the Type of Tinnitus Sensation. Journal of Clinical Psychology in Medical Settings, 23(3), 310–318. https://doi.org/10.1007/s10880-015-9444-5

3. Shargrodsky J., Curhan G.C., Farwell W.R. (2010). Prevalence and characteristics of tinnitus among US adults. The American Journal of Medicine, 123(8),711–8. https://doi.org/10.1016/j.amjmed.2010.02.015 PMID: 20670725.

4. Eggertmont J. J., & Roberts L. E. (2004). The neuroscience of tinnitus. Trends in Neurosciences, 27(11), 676–682. https://doi.org/10.1016/j.tins.2004.08.010

5. Unterrainer J., Greimal K. V., Leibetseder M., & Koller T. (2003). Experiencing tinnitus: which factors are important for perceived severity of the symptom? International Tinnitus Journal, 9(2), 130–133. https://www.ncbi.nlm.nih.gov/pubmed/15106289.

6. Moring J., Bowen A., Thomas J., & Joseph J. (2015). Acceptance Mediates the Relationship Between Tinnitus-Related Cognitions and Anxiety Sensitivity. American Journal of Audiology, 24(2), 235–242. https://doi.org/10.1044/2015_AJA-15-0006

7. Dietrich S. (2004). Earliest historic reference of ‘tinnitus’ is controversial. The Journal of Laryngology & Otology, 118(7), 487–488. https://doi.org/10.1258/0022215041615182

8. Husain F. T. (2021). Learning to control tinnitus. In Psychology of Learning and Motivation (Vol. 74, pp. 47–94). Academic Press.

9. Turkeltaub P. E., Eden G. F., Jones K. M., & Zeffiro T. A. (2002). Meta-analysis of the functional neuro-anatomy of single-word reading: method and validation. NeuroImage, 16(3 Pt 1), 765–780. https://doi.org/10.1006/nimg.2002.1131

10. Fox P. T., & Lancaster J. L. (2002). Opinion: Mapping context and content: the BrainMap model. Nature Reviews: Neuroscience, 3(4), 319–321. https://doi.org/10.1038/nn789

11. Fox P. T., Lancaster J. L., Laird A. R., & Eickhoff S. B. (2014). Meta-analysis in human neuroimaging: computational modeling of large-scale databases. Annual Review of Neuroscience, 37, 409–434. https://doi.org/10.1146/annurev-neuro-062012-170320

12. Song J. J., De Ridder D., Van de Heyning P., & Vanneste S. (2012). Mapping tinnitus-related brain activation: an activation-likelihood estimation metaanalysis of PET studies. Journal of nuclear medicine: official publication, Society of Nuclear Medicine, 53(10), 1550–1557. https://doi.org/10.2967/jnumed.112.102939

13. Arnold W., Bartenstein P., Oestreicher E., Römer W., & Schweiger M. (1996). Focal metabolic activation in the predominant left auditory cortex in patients suffering from tinnitus: a PET study with [18F] deoxyglucose. ORL: journal for oto-rhino-laryngology and its related specialties, 58(4), 195–199. https://doi.org/10.1159/000176835

14. Gardner A, Pagani M, Jacobsson H, et al. (2002) Differences in resting-state regional cerebral blood flow assessed with Tc-99m-HMPAO SPECT and brain atlas matching between depressed patients with and without tinnitus. Nuclear Medicine Communications 23(5), 429–439. https://doi.org/10.1097/00006231-200205000-00002
15. Adjamian P., Sereda M., & Hall D. A. (2009). The mechanisms of tinnitus: perspectives from human functional neuroimaging. Hearing Research, 253(1–2), 15–31. https://doi.org/10.1016/j.heares.2009.04.001

16. Lanting C. P., de Kleine E., & van Dijk P. (2009). Neural activity underlying tinnitus generation: results from PET and fMRI. Hearing Research, 255(1–2), 1–13. https://doi.org/10.1016/j.heares.2009.06.009

17. Zang Y., Jiang T., Lu Y., He Y., & Tian L. (2004). Regional homogeneity approach to fMRI data analysis. Neuroimage, 22(1), 394–400. https://doi.org/10.1016/j.neuroimage.2003.12.030

18. Zou Q. H., Zhu C. Z., Yang Y., Zuo X. N., Long X. Y., Cao Q. J., et al (2008). An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. Journal of Neuroscience Methods, 172(1), 137–141. https://doi.org/10.1016/j.jneumeth.2008.04.012

19. Ashburner J., & Friston K. J. (2000). Voxel-based morphometry—the methods. Neuroimage, 11(6 Pt 1), 805–821. https://doi.org/10.1006/nimg.2000.0582

20. Laird A. R., Fox P. M., Price C. J., Glahn D. C., Lancaster J. L., et al (2005a). ALE meta-analysis: controlling the false discovery rate and performing statistical contrasts. Human Brain Mapping, 25(1), 155–164. https://doi.org/10.1002/hbm.20136

21. Turkeltaub P. E., Eickhoff S. B., Laird A. R., Fox M., Wiener M., & Fox P. (2012). Minimizing within-experiment and within-group effects in Activation Likelihood Estimation meta-analyses. Human Brain Mapping, 33(1), 1–13. https://doi.org/10.1002/hbm.21186

22. Acar F., Seurinck R., Eickhoff S. B., & Moerkerke B. (2018). Assessing robustness against potential publication bias in Activation Likelihood Estimation (ALE) meta-analyses for fMRI. PloS One, 13(11), e0208177. https://doi.org/10.1371/journal.pone.0208177

23. Chiang F. L., Feng M., Romero R. S., Price L., Franklin C. G., Deng S., et al. (2021). Disruption of the Atrophy-based Functional Network in Multiple Sclerosis Is Associated with Clinical Disability: Validation of a Meta-Analytic Model in Resting-State Functional MRI. Radiology, 299(1), 159–166. https://doi.org/10.1148/radiol.2021203414

24. Garrett A., Cohen J. A., Zack S., Carrion V., Jo B., Blader J., et al (2019). Longitudinal changes in brain function associated with symptom improvement in youth with PTSD. Journal of Psychiatric Research, 114, 161–169. https://doi.org/10.1016/j.jpsychires.2019.04.021

25. Gray J. P., Müller V. I., Eickhoff S. B., & Fox P. T. (2020). Multimodal Abnormalities of Brain Structure and Function in Major Depressive Disorder: A Meta-Analysis of Neuroimaging Studies. The American Journal of Psychiatry, 177(5), 422–434. https://doi.org/10.1176/appi.ajp.2019.19050560

26. Müller V. I., Ceslisk E. C., Laird A. R., Fox P. T., Radua J., Mataix-Cols D., et al. (2018). Ten simple rules for neuroimaging meta-analysis. Neuroscience and Biobehavioral Reviews, 84, 151–161. https://doi.org/10.1016/j.neubiorev.2017.11.012

27. Husain F. T., Medina R. E., Davis C. W., Szymko-Bennett Y., Simonyan K., Pajor N. M., et al. (2011). Neuroanatomical changes due to hearing loss and chronic tinnitus: a combined VBM and DTI study. Brain Research, 1369, 74–88. https://doi.org/10.1016/j.brainres.2010.10.095

28. Husain F. T., & Schmidt S. A. (2014). Using resting state functional connectivity to unravel networks of tinnitus. Hearing Research, 307, 153–162. https://doi.org/10.1016/j.heares.2013.07.010

29. Husain F. T., Zimmerman B., Tai Y., Finnegan M. K., Kay E., Khan F., et al. (2019). Assessing mindfulness-based cognitive therapy intervention for tinnitus using behavioural measures and structural MRI: a pilot study. International Journal of Audiology, 58(12), 889–901. https://doi.org/10.1080/14992027.2019.1629655

30. Eickhoff S. B., Bzdok D., Laird A. R., Kurth F., & Fox P. T. (2012). Activation likelihood estimation meta-analysis revisited. Neuroimage, 59(3), 2349–2361. https://doi.org/10.1016/j.neuroimage.2011.09.017

31. Eickhoff S. B., Laird A. R., Grefkes C., Wang L. E., Zilles K., & Fox P. T. (2009). Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. Human Brain Mapping, 30(9), 2907–2926. https://doi.org/10.1002/hbm.20718

32. Fox P. T., Laird A. R., Fox S. P., Fox P. M., Uecker A. M., Crank M., et al. (2005). BrainMap taxonomy of experimental design: description and evaluation. Human Brain Mapping, 25(1), 185–198. https://doi.org/10.1002/hbm.20141

33. Laird A. R., Lancaster J. L., & Fox P. T. (2005b). BrainMap: the social evolution of a human brain mapping database. Neuroinformatics, 3(1), 65–78. https://doi.org/10.1385/ni:3:1:065

34. Vanasse T. J., Fox P. M., Barron D. S., Robertson M., Eickhoff S. B., Lancaster J. L., et al. (2018). BrainMap VBM: An environment for structural meta-analysis. Human Brain Mapping, 39(8), 3308–3325. https://doi.org/10.1002/hbm.24078

35. Moring, J. (2022, March 31). Tinnitus Meta-Analysis. osf.io/734dc.
36. Samartsidis P., Montagna S., Nichols T. E., & Johnson T. D. (2017). The coordinate-based meta-analysis of neuroimaging data. *Statistical science: a review journal of the Institute of Mathematical Statistics*, 32(4), 580–599. https://doi.org/10.1214/17-STS624

37. Boyen K., Langers D. R., de Kleine E., & van Dijk P. (2013). Gray matter in the brain: differences associated with tinnitus and hearing loss. *Hearing Research*, 295, 67–78. https://doi.org/10.1016/j.heares.2012.02.010

38. Carpenter-Thompson J. R., Akrofi K., Schmidt S. A., Dolcos F., & Husain F. T. (2014). Alterations of the emotional processing system may underlie preserved rapid reaction time in tinnitus. *Brain Research*, 1567, 28–41. https://doi.org/10.1016/j.brainres.2014.04.024

39. Chen Y. C., Zhang J., Li X. W., Xia W., Feng X., Gao B., Ju S. H., Wang J., Salvi R., & Teng G. J. et al. (2014). Aberrant spontaneous brain activity in chronic tinnitus patients revealed by resting-state functional MRI. *NeuroImage. Clinical*, 6, 222–228. https://doi.org/10.1016/j.nicl.2014.09.011

40. Chen Y.-C., Zhang J., Li X.-W., Xia W., Feng X., Qian C., Yang X.-Y., Lu C.-Q., Wang J., & Salvi R., et al. (2015). Altered intra- and interregional synchronization in resting-state cerebral networks associated with chronic tinnitus. *Neural Plasticity*, 2015. https://doi.org/10.1155/2015/475382

41. Chen Y. C., Fang F., Wang J., Bo F., Xia W., Gu J. P., & Yin X., et al. (2017). Resting-State Brain Abnormalities in Chronic Subjective Tinnitus: A Meta-Analysis. *Frontiers in Human Neuroscience*, 11, 22. https://doi.org/10.3389/fnhum.2017.00022

42. Gentil A., Deverdun J., Menjot de Cham pfleur N., Puel J.-L., Le Bars E., & Venail F. (2019). Alterations in regional homogeneity in patients with unilateral chronic tinnitus. *Trends in Hearing*, 23, 2331216519830237. https://doi.org/10.1177/2331216519830237

43. Geven L., De Kleine E., Willemsen A., & Van Dijk P. (2014). Asymmetry in primary auditory cortex activity in tinnitus patients and controls. *Neuroscience*, 256, 117–125. https://doi.org/10.1016/j.neuroscience.2013.10.015

44. Han L., Pengfei Z., Zhaohui L., Fei Y., Ting L., Cheng D., & Zhenchang W., et al. (2015). Resting-state functional connectivity density mapping of etiology confirmed unilateral pulsatile tinnitus patients: Altered functional hubs in the early stage of disease. *Neuroscience*, 310, 27–37. https://doi.org/10.1016/j.neuroscience.2015.09.032

45. Han L., Zhaohui L., Fei Y., Pengfei Z., Ting L., Cheng D., & Zhenchang W., et al. (2015). Disrupted neural activity in unilateral vascular pulsatile tinnitus patients in the early stage of disease: evidence from resting-state fMRI. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 59, 91–99. https://doi.org/10.1016/j.pnpbp.2015.01.013

46. Han L., Zhaohui L., Fei Y., Pengfei Z., Ting L., Cheng D., & Zhenchang W., et al. (2014). Abnormal baseline brain activity in patients with pulsatile tinnitus: a resting-state FMRI study. *Neural Plasticity*, 2014, 549162. https://doi.org/10.1155/2014/549162

47. Han Q., Zhang Y., Liu D., Wang Y., Pengfei Z., & Wang J. (2018). Disrupted neural activity and functional connectivity in subjective tinnitus patients: evidence from resting-state fMRI data. *Neurodiagnostics*, 60(11), 1193–1201. https://doi.org/10.1007/s00234-018-2087-0 PMID: 30159629

48. Laureano M. R., Onishi E. T., Bressan R. A., Castiglioni M. L. V., Batista I. R., Reis M. A., Garcia M. V., de Andrade A. N., de Almeida R. R., & Garrido G. J., et al. (2014). Memory networks in tinnitus: a functional MRI study. *NeuroImage*, 92, e87839. https://doi.org/10.1016/j.neuroimage.2008735 PMID: 24516567

49. Leaver A. M., Seydell-Greenwald A., Turesky T., Morgan S., Kim H. J., & Rauschecker J. P. (2012). Cortico-imbic morphology separates tinnitus from tinnitus distress. *Frontiers in Systems Neurosciences*, 6, 21. https://doi.org/10.3389/fnsys.2012.00021 PMID: 22493571

50. Leaver A. M., Turesky T. K., Seydell-Greenwald A., Morgan S., Kim H. J., & Rauschecker J. P. (2016). Intrinsic network activity in tinnitus investigated using functional MRI. *Human Brain Mapping*, 37(8), 2717–2735. https://doi.org/10.1002/hbm.23204 PMID: 27081485

51. Liu Y., Lv H., Zhao P., Liu Z., Chen W., Gong S., Wang Z., & Zhu J.-M., et al. (2018). Neuroanatomical alterations in patients with early stage of unilateral pulsatile tinnitus: a voxel-based morphometry study. *Neural Plasticity*, 2018. https://doi.org/10.1155/2018/4756471 PMID: 29681925

52. Lv H., Zhao P., Liu Z., Li R., Zhang L., Wang P., Yan F., Liu L., Wang G., & Zeng R., et al. (2017). Abnormal regional activity and functional connectivity in resting-state brain networks associated with etiology confirmed unilateral pulsatile tinnitus in the early stage of disease. *Hearing Research*, 346, 55–61. https://doi.org/10.1016/j.heares.2017.02.004 PMID: 28188881

53. Maudoux A., Lefebvre P., Cabay J. E., Demertzii A., Vanhaudenhuyse A., Laureys S., & Soddu A., et al. (2012). Auditory resting-state network connectivity in tinnitus: a functional MRI study. *PloS One*, 7(5), e36222. https://doi.org/10.1371/journal.pone.0036222 PMID: 22574141
54. Melcher J. R., Knudson I. M., & Levine R. A. (2013). Subcallosal brain structure: correlation with hearing threshold at supra-clinical frequencies (> 8 kHz), but not with tinnitus. *Hearing Research*, 295, 79–86. https://doi.org/10.1016/j.heares.2012.03.013 PMID: 22504034

55. Mühlau M., Rauschecker J., Oestreich E., Gaser C., Röttinger M., Wohlschlager A., Simon F., Etgen T., Conrad B., & Sander D., et al. (2006). Structural brain changes in tinnitus. *Cerebral Cortex*, 16(9), 1283–1288. https://doi.org/10.1093/cercor/bjh070 PMID: 16280464

56. Schmidt S. A., Zimmermann B., Medina R. O. B., Carpenter-Thompson J. R., & Husain F. T. (2018). Changes in gray and white matter in subgroups within the tinnitus population. *Brain Research*, 1679, 64–74. https://doi.org/10.1016/j.brainres.2017.11.012 PMID: 29158175

57. Seydell-Greenwald A., Leaver A. M., Turesky T. K., Morgan S., Kim H. J., & Rauschecker J. P. (2012). Functional MRI evidence for a role of ventral prefrontal cortex in tinnitus. *Brain Research*, 1485, 22–39. https://doi.org/10.1016/j.brainres.2012.08.052 PMID: 22982009

58. Vanneste S., Van De Heyning P., & De Ridder D. (2015). Tinnitus: a large VBM-EEG correlational study. *PloS One*, 10(3), e0115122. https://doi.org/10.1371/journal.pone.0115122 PMID: 25781934

59. Yang H., Zheng Y., Ou Y., & Huang X. (2014). Regional homogeneity on resting state fMRI in patients with tinnitus. *Journal of Otology*, 9(4), 173–178. https://doi.org/10.1016/j.joto.2014.10.001

60. Zhou G.-P., Shi X.-Y., Wei H.-L., Qu L.-J., Yu Y.-S., Zhou Q.-Q., Yin X., Zhang H., & Tao Y.-J., et al. (2019). Disrupted intraregional brain activity and functional connectivity in unilateral acute tinnitus patients with hearing loss. *Frontiers in Neuroscience*, 13, 1010. https://doi.org/10.3389/fnins.2019.01010 PMID: 31607851

61. Woodward N. D., & Cascio C. J. (2015). Resting-State Functional Connectivity in Psychiatric Disorders. *JAMA Psychiatry*, 72(8), 743–744. https://doi.org/10.1001/jamapsychiatry.2015.0484 PMID: 26061674

62. Schmidt S. A., Akrofi K., Carpenter-Thompson J. R., & Husain F. T. (2013). Default mode, dorsal attention and auditory resting state networks exhibit differential functional connectivity with hearing loss. *PloS One*, 8(10), e76488. https://doi.org/10.1371/journal.pone.0076488 PMID: 24098513

63. Buckner R. L., Krienen F. M., & Yeo B. T. (2013). Opportunities and limitations of intrinsic functional connectivity MRI. *Nature Neuroscience*, 16(7), 832–837. https://doi.org/10.1038/nn.3423 PMID: 23799476

64. Buckner R. L., Andrews-Hanna J. R., & Schacter D. L. (2008). The brain’s default network: anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences*, 1124, 1–38. https://doi.org/10.1196/annals.1440.011 PMID: 18400922

65. Greicius M. D., Supekar K., Menon V., & Dougherty R. F. (2009). Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cerebral Cortex*, 19(1), 72–78. https://doi.org/10.1093/cercor/bhn059 PMID: 18403396

66. Laird A. R., Fox P. M., Eickhoff S. B., Turner J. A., Ray K. L., McKay D. R.,… Fox P. T., et al. (2011). Behavioral Interpretations of Intrinsic Connectivity Networks. *Journal of Cognitive Neuroscience*, 23(12), 4022–4037. https://doi.org/10.1162/jocn_a_00077 PMID: 21671731.

67. Leech R., Kamourie S., Beckmann C. F., & Sharp D. J. (2011). Fractionating the default mode network: distinct contributions of the ventral and dorsal posterior cingulate cortex to cognitive control. *Journal of Neuroscience*, 31(9), 3217–3224. https://doi.org/10.1523/JNEUROSCI.5626-10.2011 PMID: 21368033

68. Smith M. S., Fox P. T., Miller K. L., Glahn D. C., Fox P. M., Mackay C. E.,… Beckmann C. F., et al (2009). Correspondence of the brain’s functional architecture during activation and rest. *Proceedings of the National Academy of Sciences of the United States of America*, 106(31), 13040–13045. https://doi.org/10.1073/pnas.0905267106 PMID: 19620724

69. Leech R., & Smallwood J. (2019). The posterior cingulate cortex: Insights from structure and function. *Handbook of Clinical Neurology*, 166, 73–85. https://doi.org/10.1016/B978-0-444-64196-0.00005-4 PMID: 31731926

70. Maddock R. J., Garrett A. S., & Buonocore M. H. (2001). Remembering familiar people: the posterior cingulate cortex and autobiographical memory retrieval. *Neuroscience*, 104(3), 667–676. https://doi.org/10.1016/s0068-6848(01)00108-7 PMID: 11440800

71. Busler J. N., Yanes J. A., Bird R. T., Reid M. A., & Robinson J. L. (2019). Differential functional patterns of the human posterior cingulate cortex during activation and deactivation: a meta-analytic connectivity model. *Experimental Brain Research*, 237(9), 2367–2385. https://doi.org/10.1007/s00221-019-05595-y PMID: 31292696

72. McKenna L., Marks E. M., Hallsworth C. A., & Schaette R. (2017). Mindfulness-Based Cognitive Therapy as a Treatment for Chronic Tinnitus: A Randomized Controlled Trial. *Psychotherapy and Psychosomatics*, 86(6), 351–361. https://doi.org/10.1159/000478267 PMID: 29131084
73. Leaver A. M., Renier L., Chevillet M. A., Morgan S., Kim H. J., & Rauscher 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 PMID: 21220097

74. Samartsidis P., Montagna S., Laird A.R., Fox P.T., Johnson T.JD., & Nichols T.E. (2019). Estimating the prevalence of missing experiments in a neuroimaging meta-analysis. *bioRxiv*. https://doi.org/10.1101/225425

75. Farhadi M., Mahmoudian S., Saddadi F., et al. (2010) Functional brain abnormalities localized in 55 chronic tinnitus patients: fusion of SPECT coincidence imaging and MRI. *Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism*, 30, 864–870. https://doi.org/10.1038/jcbfm.2009.254 PMID: 20068582

76. Cabeza R., & Nyberg L. (2000). Imaging cognition II: An empirical review of 275 PET and fMRI studies. *Journal of Cognitive Neuroscience*, 12(1), 1–47. https://doi.org/10.1162/089892902317362029 PMID: 10769304

77. Tranel D., Damasio H., & Damasio A. R. (1997). A neural basis for the retrieval of conceptual knowledge. *Neuropsychologia*, 35(10), 1319–1327. https://doi.org/10.1016/s0028-3932(97)00085-7 PMID: 9347478

78. Cheng S., Xu G., Zhou J., Qu Y., Li Z., He Z.,... Liang F., et al. (2020). A Multimodal Meta-Analysis of Structural and Functional Changes in the Brain of Tinnitus. *Frontiers in Human Neuroscience*, 14, 28. https://doi.org/10.3389/fnhum.2020.00028 PMID: 32161526

79. Mohan A., De Ridder D., Idiculla R., D. S. C, & Vanneste S. (2018). Distress-dependent temporal variability of regions encoding domain-specific and domain-general behavioral manifestations of phantom perceptions. *European Journal of Neuroscience*, 48(2), 1743–1764. https://doi.org/10.1111/ejn.13988 PMID: 29888410

80. Corbetta M., Kincade J. M., & Shulman G. L. (2002). Neural systems for visual orienting and their relationships to spatial working memory. *Journal of Cognitive Neuroscience*, 14(3), 508–523. https://doi.org/10.1162/089892902317362029 PMID: 11970810

81. Carpenter-Thompson J. R., Schmidt S. A., & Husain F. T. (2015). Neural Plasticity of Mild Tinnitus: An fMRI Investigation Comparing Those Recently Diagnosed with Tinnitus to Those That Had Tinnitus for a Long Period of Time. *Neural Plasticity*, 2015, 161478. https://doi.org/10.1155/2015/161478 PMID: 26246914

82. Schmidt S. A., Carpenter-Thompson J., & Husain F. T. (2017). Connectivity of precuneus to the default mode and dorsal attention networks: A possible invariant marker of long-term tinnitus. *Neuroimage: Clinical*, 16, 196–204. https://doi.org/10.1016/j.nicl.2017.07.015 PMID: 28794980

83. Frangou S. (2010). Cognitive function in early onset schizophrenia: a selective review. *Frontiers in Human Neuroscience*, 3, 79. https://doi.org/10.3389/neuro.09.079.2009 PMID: 20140271

84. Frascarelli M., Tognini S., Mirigliani A., Parente F., Buzzanca A., Torti M. C.,... Fusar-Poli P., et al. (2015). Medial frontal gyrus alterations in schizophrenia: relationship with duration of illness and executive dysfunction. *Psychiatry Research*, 231(2), 103–110. https://doi.org/10.1016/j.psychres.2014.10.017 PMID: 25498920

85. Henry J. A., Roberts L. E., Caspary D. M., Theodoroff S. M., & Salvi R. J. (2014). Underlying mechanisms of tinnitus: review and clinical implications. *Journal of the American Academy of Audiology*, 25(1), 5–22. https://doi.org/10.3766/jaaa.25.1.2 PMID: 24622858

86. Møller A. R. (2007). The role of neural plasticity in tinnitus. *Progress in Brain Research*, 166, 37–45. https://doi.org/10.1016/S0079-6123(07)60003-6 PMID: 17967699

87. Norena A. J. (2015). Revisiting the cochlear and central mechanisms of tinnitus and therapeutic approaches. *Audiology & Neuro-Otology*, 20 Suppl 1, 53–59. https://doi.org/10.1159/000380749 PMID: 25997584

88. Ryan D., & Bauer C. A. (2016). Neuroscience of Tinnitus. *Neuroimaging Clinics of North America*, 26(2), 187–196. https://doi.org/10.1016/j.nic.2015.12.001 PMID: 27154602