Research article

Functional brain changes in auditory phantom perception evoked by different stimulus frequencies

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\section*{A R T I C L E  I N F O}

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- Connectivity
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- Prediction error
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\section*{A B S T R A C T}

Bayesian models of brain function such as active inference and predictive coding offer a general theoretical framework with which to explain several aspects of normal and disordered brain function. Of particular interest to the present study is the potential for such models to explain the pathology of auditory phantom perception, i.e. tinnitus. To test this framework empirically, we perform an fMRI experiment on a large clinical sample ($n = 75$) of the human chronic tinnitus population. The experiment features a within-subject design based on two experimental conditions: subjects were presented with sound stimuli matched to their tinnitus frequency (TF) as well as similar stimuli presented at a control frequency (CF). The responses elicited by these stimuli, as measured using both activity and functional connectivity, were then analyzed both within and between conditions. Given the Bayesian-brain framework, we hypothesize that TF stimuli will elicit greater activity and/or functional connectivity in areas related to the cognitive and emotional aspects of tinnitus, i.e. tinnitus-related distress. We conversely hypothesize that CF stimuli will elicit greater activity/connectivity in areas related to auditory perception and attention. We discuss our results in the context of this framework and suggest future directions for empirical testing.

\section*{1. Introduction}

Tinnitus is defined as the perception of sound, typically tones and/or noise, in the absence of a corresponding, external source [1,2]. Since the advent of the neurophysiological model of tinnitus [3], our conception of the disorder has shifted from it being a purely cochlear problem to being a complex pathology of both auditory and non-auditory brain areas and networks [2,4–7]. Phantom perception of sound is often compared to phantom pain [8] and there is a growing body of evidence to suggest that the two disorders are linked [9]. Additionally, an emerging theoretical framework that describes the brain as a prediction machine potentially offers a basis with which to describe not only tinnitus and phantom pain but also several other disorders of phantom perception as maladapted processes of active (Bayesian) inference and predictive coding; see e.g. [4,10,11]. The specific aim of the present study is to test this framework empirically in a clinical sample of the tinnitus population.

We hypothesize that the predictive-brain framework can explain the pathology of tinnitus [4,10,11], and our model is as follows. First, sensory deafferentation, in this case hearing loss, elicits a prediction error in the auditory system. This prediction error arises because the brain’s internal model predicts, but no longer receives, a certain level of auditory input in the deafferented pathway [4]; the prediction in question is a parameter of the prior density over inputs, namely the prior expectation [12]. Because this change in input is statistically reliable—hearing loss is generally permanent, after all—the brain updates its internal model using active (Bayesian) inference to better describe the new distribution of sensory input [13–16]. “Updating” in this case means that the sensitivity of the deafferented cells is increased [17,18], which enables a lower level of neuronal activity to update the model and thus affect perception. However, if these changes are sufficient to allow spontaneous activity in the deafferented cells to update the model, then that noise is treated as signal and thus perceived [11]. In other words, the brain resolves the prediction error resulting from hearing loss but in doing so it learns a causal relationship between spontaneous activity (input) and auditory perception (cause), which
manifests as a phantom percept. This is an example of maladaptive Bayesian belief updating [10].

Two sounds that differ in frequency but are otherwise identical (e.g. pure tones) should elicit similar neural responses in a healthy brain, barring the difference reflecting the change in frequency itself. However, given our model, we would expect tinnitus-frequency sounds to evoke a different neural response than similar sounds at other frequencies because the maladapted internal model of the tinnitus brain has a prior expectation of the tinnitus percept. In other words, a tinnitus-frequency stimulus should evoke minimal prediction error in perceptual areas—and, in turn, minimal belief updating—because the maladapted model already predicts a similar input. The opposite may be true elsewhere in the brain, such as in areas with a role in the cognitive and emotional components of tinnitus, i.e. tinnitus-related distress.

Previous research suggests that a patient’s psychological and emotional state can have a powerful impact on tinnitus perception [19–22]. While sound, unlike pain, is not intrinsically aversive, an estimated 20% of tinnitus patients—1–3% of the general population [2]—report that tinnitus negatively impacts their quality of life. According to the pain literature, modulation of the affect of the pain percept occurs due to a reappraisal of emotional experiences of perception, which is reflected by prefrontal cortex (PFC) communicating with nucleus accumbens (NAc) and the amygdala [23,24]. Increased functional connectivity between NAc and PFC has also predicted the persistence of pain, which implies a causal relationship between corticostriatal circuits and pain chronification [25]. Additional cortical and subcortical regions, including reward/motivation circuits, integrate internal and external signals and encode these signal valuations, while corticobulbar structures engage during the anticipation of the percept [26]. The role of the NAc, mediated by ventral tegmental area (VTA) dopaminergic inputs, appears to be signaling the salience and affective value of incoming stimuli [23,27]. This information is then projected to areas of the frontal lobe such as the ventromedial prefrontal cortex (vmPFC), pregenual anterior cingulate cortex (pgACC), and dorsal anterior cingulate cortex (dACC) that are involved in learning of aversive outcomes and encoding information about the value of a chosen action [28,29].

Tinnitus-related distress appears to be related to functional changes in a disorder-general network involving the amygdala, hippocampus, parahippocampal cortex (PHC), insular cortex, and subgenual ACC (sgACC) [8]. In these areas, we would expect tinnitus-frequency sounds to elicit a greater response than sounds at other frequencies for the simple reason that the latter sounds generally do not have a negative valence. The response in these areas to non-tinnitus sounds should be attenuated either because they mask tinnitus perception and/or because they serve as a distractor, i.e. drawing attention away from the tinnitus percept.

The present study is designed to test our hypotheses directly using an fMRI experiment. We present human chronic tinnitus patients with sounds matched to their tinnitus frequency (TF) and with sounds at a control frequency (CF) while they undergo scanning. We analyze BOLD activity at the whole-brain level as well as in specific regions of interest (ROIs) chosen based on the existing tinnitus literature. Furthermore, we analyze functional connectivity between these ROIs to observe changes at the network level. We hypothesize that TF stimuli will elicit greater activity and functional connectivity specifically in areas related to cognitive and emotional, but not perceptual, aspects of tinnitus. This includes frontostriatal networks [9,25] as well as regions of the general distress network proposed in [8]: amygdala, PHC, insular cortex, and sgACC. Outside of these regions, we hypothesize that CF stimuli will elicit greater activity and functional connectivity.

2. Materials and methods

The present study is a retrospective analysis of data collected in a clinical context. Tinnitus patients were recruited at the University Hospital of Antwerp and referred to the Catholic University of Leuven for MR scanning. All participants provided written informed consent that their data could be used for research purposes per the Declaration of Helsinki. The study was approved by the ethical committee of the University Hospital of Antwerp (IRB: UZA OGA8S) and was carried out in accordance with the approved guidelines.

2.1. Subjects

The subject group consisted of humans with clinically relevant tinnitus (n = 75), defined as being severe enough for the patient to voluntarily seek out treatment [30]. The subjects’ ages ranged from 19 to 72 years with a mean age of 51.0 ± 11.9 (SD). 28.0% of subjects were female (n = 21). 54.7% of subjects reported that their tinnitus percepts were noise-like (n = 41) while 45.3% reported pure-tone percepts (n = 34). 46.7% of subjects (n = 35) reported unilateral tinnitus, with 28.0% left-lateralized (n = 21) and 18.7% right-lateralized (n = 14), while 53.3% of subjects reported bilateral or holocranial tinnitus (n = 40). Subjects reported tinnitus-related distress using the Tinnitus Questionnaire (TQ), which is scored 0–82 with higher scores corresponding to greater levels of distress [31,32]; the mean TQ score was 49.3 ± 16.4 (SD). All subjects were right-handed.

2.2. Audiology

Before scanning, subjects were screened using pure-tone audiometry to check for hearing loss and to determine any necessary level correction for the experimental stimuli. All patients were screened for the extent of hearing loss, in dB HL, at 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz using pure tone audiometry. This was done per the recommended British Society of Audiology procedures, i.e. pure tone air and bone conduction threshold audiometry, with and without masking, plus determination of uncomfortable loudness levels. Fig. 1 shows the mean hearing thresholds for the left and right ears for all tinnitus subjects.

2.3. Stimulus frequency selection

A pitch-matching procedure was used to determine behaviorally each subject’s tinnitus percept frequency. First, a 1-kHz pure tone was presented contralaterally to the tinnitus ear at a level 10 dB above the patient’s hearing threshold in that ear (or the worse ear, in the patients with bilateral or holocranial tinnitus). The frequency of the tone was then adjusted until the patient judged the sound to resemble his/her tinnitus most. This frequency was, on average, 5.29 ± 3.38 (SD) kHz. The stimulus level was adjusted along with frequency to maintain a 10-dB difference above each patient’s hearing threshold. Both stimulus level and frequency were checked again within the scanner before starting the experiment.

2.4. Experimental procedure

The fMRI experiment consisted of a blocked design of 18 epochs of 30 s each. We presented subjects with three different auditory stimuli binaurally: white noise through a bandpass filter with a 1000-Hz half width (f ± 1000 Hz); white noise through a bandpass filter with a 500-Hz half width (f ± 500 Hz); a pure tone (f). The center frequencies of the bandpass filters were the same frequency as that of the pure tone. Stimuli were presented in bursts coinciding with the silent gaps between fMRI volume acquisitions, with one stimulus per burst and six epochs per stimulus. Subjects were scanned twice per this design, each at a different frequency, f. We presented the stimuli to each subject at their tinnitus percept frequency (TF)—chosen via the procedure described in Section 3.3—and at a control frequency (CF) at least one octave higher or lower than the tinnitus frequency; this frequency was, on average, 1.74 ± 1.31 (SD) kHz. The decision to use a higher or lower CF was made on an individual basis such that subjects with a high TF had a low CF and vice versa; only 21.3% of subjects (n = 16) had a
CF higher than their TF. The TF/CF presentation order was randomized per subject. Subjects were instructed to listen to the stimuli attentively with their eyes closed. A test run was performed before the start of the experiment to make sure that subjects could hear the stimuli well despite the background scanner noise, which can reach levels of up to 110 dB SPL [33]. All stimuli were presented binaurally through headphones. The headphones were dedicated for use in an MRI scanner, attenuating scanner noise by approximately 30 dB.

2.5. Image acquisition and preprocessing

The MRI scans were performed in a Philips 3 T MRI scanner with an eight-channel phased-array head coil. For the functional imaging, a T2*-weighted single shot gradient echo (GE) echo-planar imaging (EPI) sequence was used with an echo time (TE) and repetition time (TR) of 33 and 5000 ms, respectively (acquisition matrix = 80 × 80; field of view = 230 × 230 × 256 2 mm; reconstructed voxel size = 2.88 × 2.88 × 4.00 mm). A clustered volume acquisition technique was used in which the acquisition time (TA) was shorter than the TR, namely 2000 ms, leaving a 3000 ms silent gap in between each EPI volume acquisition. A sensitivity encoding (SENSE) reduction factor of 2.5 was used in the anterior-posterior direction. 32 contiguous, transverse slices of 4 mm thickness each were acquired during 108 dynamics. This resulted in a total scan time of 9 min 30 s per session.

For anatomical reference, an additional high-resolution 3D T1-weighted turbo field echo (TFE) sequence was used with a TE/TR of 4.60/9.60 ms and an acquired voxel size of 0.98 × 0.98 × 1.20 mm³ (acquisition matrix = 256 × 256; field of view = 250 × 250 × 218 mm³; reconstructed voxel size = 0.98 × 0.98 × 1.20 mm). SENSE reduction factors of 1.5 and 2 were used in the right-left direction and the anterior-posterior direction, respectively. 182 contiguous, coronal slices of 4 mm thickness each were acquired during 108 dynamics. This resulted in a total scan time of 9 min 30 s per session.

Image preprocessing was carried out using SPM12, a third-party software toolbox for Matlab (The MathWorks Inc., Natick, MA) created by the Wellcome Trust Centre for Neuroimaging (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). The anatomical reference image for each subject was skull-stripped and the origin was manually defined at the anterior commissure. The functional image preprocessing pipeline included the following steps: motion correction in six directions; coregistration of functional and structural volumes using a normalized mutual information objective function; normalization of all volumes to MNI standard space; spatial smoothing of functional volumes using an 8-mm full-width at half maximum (FWHM) Gaussian kernel.

2.6. Analysis

2.6.1. Whole-brain analysis

We analyzed the preprocessed images at the subject level in SPM12. This was done by specifying a general linear model (GLM) design matrix, estimating the parameters for each subject using the restricted maximum likelihood (ReML) method, and generating statistical parametric maps (SPMs). There were ten GLM regressors, including three for the stimuli (WBN, NBN, and PT), six for head motion correction (x, y, z, pitch, roll, and yaw), plus a constant. We analyzed the subject-level SPMs at the group level using one-sample t-tests. We then analyzed the specified designs using ReML to generate a group-level SPM. We checked the t scores at each voxel in that group-level SPM for significance at the 0.05 level by calculating the corresponding p values, correcting for multiple comparisons at the voxel level using the false discovery rate (FDR) adjustment [34]. We used xjview (http://www.alivelearn.net/xjview/) to perform FDR correction and to detect peak regions. We used Python to plot the results using a glass-brain visualizer.

2.6.2. ROI analysis

We chose regions of interest (ROIs) based on their relevance to tinnitus and to our model. Given that the present study is focused on tinnitus, i.e., phantom auditory perception, the inclusion of primary auditory cortex (A1) is self-explanatory. In tinnitus, when missing auditory information cannot be retrieved directly from sensory cortex, e.g., in cases of severe hearing loss, PHC is proposed to retrieve the information from memory instead [4]. Posterior cingulate cortex (PCC) is also implicated in tinnitus, especially its connection to the auditory cortex [35]. PCC is also one of the core nodes of the default network and involved with memory, making its potential interactions with PHC interesting in the context of the present study. We also chose a number of ROIs based on their involvement in signaling salience and/or affective value of incoming stimuli. These included: anterior insular cortex (AIC) and dACC, the two core nodes of the salience network [36]; NAc and VTA, two core nodes of the midbrain dopaminergic system; the hubenula (HB), another reward-signaling region [37]; the amygdala, which is most notably involved in signaling negative affect (fear, anxiety, etc.). We did not include a ROI for vmPFC because its boundaries are somewhat ill-defined. Instead, we chose to include both pgACC and
sgACC, which are more clearly defined regions that abut vmPFC and are included in some definitions of vmPFC; see e.g. “vmPFC/scACC” in [9] (subcallosal ACC = subgenual ACC). PgACC is also of specific relevance to our model given its reported involvement in encoding the value of actions [28,29] and in maintaining predictions [38].

We created spherical ROIs (n = 19) with a radius of 3 mm, or 1 mm for Hb, using the MarsBaR toolbox [39]. We used term-based meta-analyses via Neurosynth (http://neurosynth.org) to search for specific regions and chose our center coordinates based on the voxels that had the highest z-score and then either inverting the x-coordinate to obtain the contralateral ROI or using x = 0 for our midline ROIs (i.e. pgACC, sgACC, and PCC). For example, a search for “auditory cortex” shows a z-score of 21.57 at (-52, -20, 6), i.e. left A1, and so our two A1 ROIs are located at (± 52, -20, 6). The centers of the ROIs for the four smallest anatomical structures—the amygdala, Hb, NAc, and VTA—were identified manually at the subject level using the corresponding anatomical reference images in individual space, i.e. after performing realignment and coregistration but before normalization and smoothing. This was done to preserve the blood oxygen level-dependent (BOLD) signal changes measured in these structures, which are too small to be robust against the normalization and smoothing processes. The coordinates of the centers of all ROIs are presented in Table 1 except for those of the four smallest structures, which are presented separately in Supplementary Table 1.

We obtained ROI-level data by extracting the beta values of the three stimulus regressors in the GLM (i.e. WBN, NBN, and PT) from the voxels of each ROI, which we then averaged across all 108 scans within a session for each subject. We analyzed the group-level distributions of this data in SPSS using a repeated-measures ANOVA, comparing the responses to tinnitus-frequency (TF) and control-frequency (CF) stimulation. All results were checked for significance at the 0.05 level, including the Bonferroni correction for multiple comparisons where n = 19 ROIs.

2.6.3. ROI–ROI functional connectivity analysis

We analyzed functional connectivity between ROIs using partial correlations (Matlab partialcorr: https://www.mathworks.com/help/stats/partialcorr.html). We calculated these separately for TF and CF, controlling for the effect of tinnitus-related distress (TQ), to analyze the main effect of stimulus frequency. We checked all results for significance at the 0.05 level, including the FDR correction for multiple comparisons, using the method in [40] (Matlab mafdr: https://www.mathworks.com/help/bioinfo/ref/mafdr.html). We treated those partial correlations that survived FDR correction as functional connections, which we then visualized as graphs using NeuroMarVL (http://immersive.erc.monash.edu.au/neuromarvl/). The exact magnitudes of each surviving connection are presented separately in heat-map form (Matlab HeatMap: https://www.mathworks.com/help/bioinfo/ref/heatmap.html). Furthermore, we compared partial correlations between conditions by performing Fisher’s Z transformation on the results from each condition, subtracting the Z scores, and then checking the AZ values for significance at the FDR-corrected 0.05 level [40]. See also Ref [41], for further analyses based on tinnitus-related distress. As a precautionary measure, we also checked for differences in connectivity according to gender as well as perceived tinnitus location (i.e. unilateral left, right, or bilateral/holocranial) using the same subtraction analysis method; these analyses returned no significant differences in connectivity.

3. Results

Whole-brain subtraction analysis showed that, during TF stimulation, subjects had greater BOLD activity in several regions, mainly in frontal cortex, parietal cortex, and the cerebellum in comparison to CF. No regions showed greater BOLD activity during CF. See Fig. 2 for a summary visualization of the results and Table 2 for the specific t scores and p values at the peak voxels of each cluster. In our ROI-level activity analysis, we observed greater activity in response to TF vs. CF stimulation only in left Hb; this result however did not survive Bonferroni correction for multiple comparisons. We did not observe any significant differences in activity in response to CF vs. TF stimulation. See Table 3 for the full results of this analysis.

Analyses of ROI–ROI functional connectivity produced several results. While both TF and CF stimuli elicited strong functional connectivity between several of our ROIs, CF elicited more connectivity by far in terms of degree (Figs. 3, 4). Subtraction analysis shows that nearly all of the tested connections are significantly different between the two conditions even after correcting for multiple comparisons (Fig. 5). Furthermore, the majority of these differences indicate that CF elicits greater functional connectivity between our ROIs. We do observe greater TF connectivity between right A1 and left dACC, left Hb, right NAc, PCC, and sgACC. There are also several regions where the differences are lateralized. We see this, for example, in connections with bilateral A1, which has stronger connections to dACC and Hb in the left hemisphere during CF and in the right hemisphere during TF. There are also several lateralized differences in the amygdalar connectivity, including with NAc, PCC, pgACC, and VTA. Furthermore, right VTA has stronger TF connectivity with dACC, Hb, and left NAc. Bilateral VTA features stronger TF connectivity for several regions, as well, including left amygdala, right NAc, and bilateral PHC. However, to reiterate, the majority of the observed differences in connectivity are greater during CF than TF stimulation.

4. Discussion

The aim of the present study was to examine changes in the brains of chronic tinnitus patients in response to tinnitus-frequency (TF) and control-frequency (CF) sound stimuli, as measured using fMRI. Under the predictive-brain framework, we hypothesized that TF stimuli would evoke less activity/connectivity in areas related to auditory perception and more activity/connectivity in areas related to the cognitive and emotional aspects of tinnitus, e.g. tinnitus-related distress. We hypothesized the opposite pattern in response to CF stimuli. Our results are consistent with these hypotheses in some instances and less so in others. We discuss those results in more depth here in an effort to refine our hypotheses and to suggest how future studies might improve upon the present design to explore these ideas further.

Looking first at the whole-brain analyses, subtraction of the responses during TF and CF stimulation reveals several areas with increased activity. During TF stimulation, subjects exhibit greater activity in the lateral surfaces of frontal cortex—especially in the middle and inferior frontal gyri of the left hemisphere—and the cerebellum as well as in the right orbitofrontal, right parietal, and left middle temporal cortices. Many of these TF-activated regions resemble an extended

Table 1

<table>
<thead>
<tr>
<th>Region</th>
<th>Hemisphere</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auditory cortex</td>
<td>Left/Right</td>
<td>± 52</td>
<td>−20</td>
<td>6</td>
</tr>
<tr>
<td>Anterior cingulate cortex</td>
<td>Left/Right</td>
<td>± 6</td>
<td>24</td>
<td>38</td>
</tr>
<tr>
<td>Dorsal ACC</td>
<td>Midline</td>
<td>0</td>
<td>38</td>
<td>4</td>
</tr>
<tr>
<td>Prefrontal ACC</td>
<td>Midline</td>
<td>0</td>
<td>26</td>
<td>−10</td>
</tr>
<tr>
<td>Subgenual ACC</td>
<td>Midline</td>
<td>0</td>
<td>53</td>
<td>26</td>
</tr>
<tr>
<td>Posterior cingulate cortex</td>
<td>Midline</td>
<td>± 30</td>
<td>22</td>
<td>−2</td>
</tr>
<tr>
<td>Anterior insula</td>
<td>Left/Right</td>
<td>± 26</td>
<td>−36</td>
<td>−10</td>
</tr>
<tr>
<td>Parahippocampal cortex</td>
<td>Left/Right</td>
<td>± 26</td>
<td>−36</td>
<td>−10</td>
</tr>
</tbody>
</table>

ROIs listed with ‘Left/Right’ hemisphere are two separate regions with the same y and z coordinates. Coordinates for the amygdala, Hb, NAc, and VTA were chosen manually for each subject based on visual inspection of the anatomical reference images and are not in MNI space; see Table S1 for these coordinates. There are 19 ROIs in total. All ROIs are 3-mm spheres except for the Hb ROIs, which are 1-mm spheres.
cortical network for semantic cognition, which involves the representation and control of semantic knowledge [42]. This is of interest to the present study because semantic knowledge includes the meaning of sounds. While TF stimuli are less novel to tinnitus patients than CF stimuli, at least hypothetically, they should also have more meaning, given their similarity to the tinnitus percept and the presence of tinnitus-related distress. Outside of this network, orbitofrontal cortex plays a documented role in emotion as well as cognition. Taken together, our results appear to indicate that TF stimuli do elicit greater activity in areas relating to cognitive and emotional aspects of tinnitus.

With that said, the regions observed in our activity analyses do not include the regions that we had specifically hypothesized. Furthermore, none of the voxels that exhibited greater activity during CF survived correction for multiple comparisons. This is reflected in our ROI-level activity analysis, which returned no positive results for TF or CF after correction for multiple comparisons. Therefore, our activity analyses ultimately produced mixed results. One possible explanation is that the TF and CF stimuli, which were identical except for their frequencies, were too similar to elicit differences of the magnitude that we had expected. If the differences are present and merely small in terms of effect size, a larger number of subjects would raise statistical power and potentially allow more of those voxels to survive correction for multiple comparisons. We might also increase the effect sizes themselves by more closely matching the TF stimuli to the tinnitus percept and/or by making the difference between TF and CF stimuli more pronounced yet still similar enough to serve as a within-subject control, as in the present study. Incorporating any—or ideally all—of these approaches would likely produce more definitive results.

Our analyses of ROI-ROI functional connectivity produced several results, many of which were unexpected. The most striking difference
between the TF and CF conditions is that CF stimulation elicits a much higher degree of connectivity between our ROIs. This is evident even when looking at the results within each condition but especially when looking at the subtraction analysis between conditions. There are two possible explanations for this, the first of which comes from our activity analyses: our a priori choice of ROIs did not overlap with the areas which featured greater activity during TF vs. CF stimulation. Secondly, if the TF-related increases in connectivity are due to tinnitus-related distress, then our choice of TQ score as a covariate would have blunted those effects. We used TQ score as a covariate to mitigate the potentially confounding influence of tinnitus-related distress on our analyses, but this necessarily limits our ability to observe distress-related differences. On one hand, to the extent that this choice means that the observed differences are purely the result of perceptual prediction errors,
it makes sense that we would observe greater connectivity during CF stimulation. On the other hand, it leaves open the question of how changing levels of tinnitus-related distress affect the brains of tinnitus patients. We present some preliminary between-subjects analyses using the data from our present study in Ref. [41] but a proper analysis of distress-related differences will require a control group that features little to no distress; our data are clinical and thus naturally tend towards higher levels of distress.

5. Conclusions and future directions

Tinnitus involves many brain systems that are not explicitly auditory. This includes the aforementioned examples of the disorder-general distress network but also the salience network—anchored in dACC and AIC—and PHC, all of which were observed in the present study. These regions are observed across several brain functions and disorders. The links between tinnitus and chronic pain, for example, are already well documented in the literature [8,9]. The Bayesian brain literature potentially offers a basis with which to unify all disorders of phantom perception, i.e. as the result of the brain’s internal model adapting to sensory deafferentation [4,10,11]. Our present study offers a preliminary empirical test of this predictive-brain framework in the context of tinnitus. While our results were mixed, we propose several fruitful avenues for future research that can explore these theories in more depth.

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