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Dysregulation of limbic and auditory networks in tinnitus

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Summary

Tinnitus is a common disorder characterized by ringing in the ear in the absence of sound. Converging evidence suggests that tinnitus pathophysiology involves damage to peripheral and/or central auditory pathways. However, whether auditory system dysfunction is sufficient to explain chronic tinnitus is unclear, especially in light of evidence implicating other networks, including the limbic system. Using functional magnetic resonance imaging and voxel-based morphometry, we assessed tinnitus-related functional and anatomical anomalies in auditory and limbic networks. Moderate hyperactivity was present in the primary and posterior auditory cortices of tinnitus patients. However, the nucleus accumbens exhibited the greatest degree of hyperactivity, specifically to sounds frequency-matched to patients' tinnitus. Complementary structural differences were identified in ventromedial prefrontal cortex, another limbic structure heavily connected to the nucleus accumbens. Furthermore, tinnitus-related anomalies were intercorrelated in the two limbic regions and between limbic and primary auditory areas, indicating the importance of auditory-limbic interactions in tinnitus.

Introduction

Tinnitus is a common hearing disorder characterized by a "phantom sensation" of ringing or buzzing in one's ear in the absence of an external sound source. Although many people experience transient tinnitus-like symptoms as a result of brief loud-noise exposure (e.g., a rock concert) or stress, for an estimated 5–15% of the population tinnitus can become chronic and detrimental to quality of life (Eggermont and Roberts, 2004; Heller, 2003; Henry et al., 2005). With an even higher prevalence of tinnitus in expanding demographics, including aging individuals and recent war veterans (Department of Veterans Affairs, 2008; Henry et al., 2005), proper diagnosis and treatment of tinnitus are of growing concern.

Despite its high prevalence, there is little consensus regarding the neurophysiological origin of tinnitus. Most researchers agree that tinnitus can be linked to changes at one or more points along the peripheral and central auditory pathways (Eggermont and Roberts, 2004; Jastreboff, 1990; Møller, 2003; Rauschecker et al., 2010). Indeed, human brain imaging studies have identified tinnitus-related dysfunction in auditory areas, including the inferior colliculus (Melcher et al., 2000) and auditory cortex (Giraud et al., 1999; Lockwood et al., 1998; Plewnia et al., 2007; Reyes et al., 2002). In addition, a link between tinnitus and reorganization of central tonotopic maps has been suggested, based on MEG studies in

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humans (Mühlnickel et al., 1998; Weisz et al., 2005; Wienbruch et al., 2006) and electrophysiological investigations of animals subjected to acoustic trauma (Eggermont and Komiya, 2000; Irvine et al., 2003; Rajan et al., 1993). Many have proposed that these changes in the central auditory system result from damage to the auditory periphery; however, some cases of tinnitus without significant hearing loss seem to indicate that central auditory system dysfunction can stem from other etiologies, like head or neck injury (Henry et al., 2005; Levine et al., 2003) or may reflect the limitations of standard audiometry (Weisz et al., 2006). Conversely, peripheral hearing loss does not always lead to tinnitus (Hoffman and Reed, 2004).

While it seems, therefore, that auditory system dysfunction is necessary for tinnitus to occur, it is unclear whether auditory system damage alone is sufficient to cause chronic tinnitus, or whether additional mechanisms outside auditory-sensory regions may be involved. Clinicians have noted a relationship between tinnitus and emotional state (Dobie, 2003; Sullivan et al., 1988), which has led some researchers to propose that the limbic system may play a role in modulating or perpetuating tinnitus (Jastreboff, 1990; Rauschecker et al., 2010). Indeed, the lifetime incidence of clinical depression in tinnitus patients is estimated to be more than twice that of the national average (~35% vs. ~15%, respectively; Folmer et al., 1999), and treatment regimens that include forms of cognitive-behavioral therapy have been shown to be effective for some patients (Jastreboff, 2007; Robinson et al., 2008). However, empirical evidence of limbic system involvement in tinnitus is sparse, and these few studies that report limbic involvement implicate disparate sites: e.g., amygdala (Mirz et al., 2000; Shulman et al., 1995), hippocampus (Landgrebe et al., 2009; Lockwood et al., 1998), basal ganglia (Cheung and Larson, 2010; Lowry et al., 2004), and subcallosal regions (Mühlau et al., 2006). Thus, the exact nature of limbic system involvement in chronic tinnitus, if any, has yet to be elucidated.

In the current study, we use magnetic resonance imaging (MRI) to test our recent proposal that chronic tinnitus involves compromised limbic regulation of aberrant auditory system activity (Rauschecker et al. 2010). Using functional MRI (fMRI), we compared sound-evoked activity in individuals with and without tinnitus, in a corticostriatal limbic network as well as auditory cortex and thalamus. To assess potential differences in the grey and white matter of tinnitus patients' brains, we used voxel-based morphometry (VBM) analyses of high-resolution structural MRI, again focusing on limbic and auditory brain regions. If tinnitus pathophysiology does indeed involve impaired auditory-limbic interaction, then the strength of any limbic marker of tinnitus we identify should correlate with stimulus-evoked hyperactivity in the auditory system. Thus, the current study constitutes a first critical test of our previous model. Ultimately, we hoped to determine the nature of neural anomalies in tinnitus, improving our understanding of this common disorder and informing future treatments.

Results

Neural hyperactivity in tinnitus patients

During fMRI scans, auditory stimuli of several frequencies were presented: one matched in frequency to each patient's tinnitus (TF-matched; see Methods), and others within 2 octaves above or below the TF-matched stimulus. In this way, each tinnitus patient, and their "stimulus-matched" control participant, heard a custom set of stimuli based on the frequency of the patient's tinnitus sensation (Suppl. Table 1). We thus compared levels of stimulus-evoked function in individuals with and without tinnitus (Table 1).

When presented with TF-matched stimuli, tinnitus patients demonstrated higher fMRI signal than controls in the ventral striatum, specifically the nucleus accumbens (NAc; $p_{(corr)} <$

0.05, Figure 1A,B). Though a similar trend was present for all stimulus frequencies in separate ROI analyses, these differences were not significant ($p_{(corr)} > 0.05$, Bonferroni-corrected for the number of tests performed, i.e., 5). Thus, NAc hyperactivity in tinnitus patients appeared to be specific for the tinnitus frequency. Examining pairwise correlations between NAc activity and age or hearing loss clearly shows that these variables had no effect on group differences in fMRI signal (Figure 1C,D). Indeed, NAc hyperactivity in tinnitus patients was present in the single-voxel analysis (Figure 1A), in which hearing loss was a "nuisance" covariate, as well as in a separate ROI analysis, in which age was a covariate: $t_{(20)} = 5.34$, $p = 0.00004$. Additionally, NAc hyperactivity persisted in an ROI analysis restricted to the four youngest patients ($t_{(13)} = 4.98$, $p = 0.0003$), where age and hearing loss were equivalent between groups (age: $t_{(13)} = 0.99$, $p = 0.34$; mean hearing loss: $t_{(13)} = 0.64$, $p = 0.53$).

In an analysis restricted to voxels within the auditory cortex and medial geniculate nuclei (MGN; a "masked analysis", as defined in Methods), tinnitus patients exhibited greater fMRI signal than controls in bilateral posterior superior temporal gyri and sulci ($p < 0.01$, k > 108 mm^3). Hyperactivity in posterior superior temporal cortex (pSTC) was significant at the single-voxel level for all stimulus frequencies except the lowest (Table 2, *t*Figure 2A). However, in an ROI comprised of voxels exhibiting significant between-groups differences for any stimulus frequency (Figure 2B), a similar trend was observed for the lowest stimulus frequencies ($_{(20)} = 2.49$, $p = 0.02$). Tinnitus patients also demonstrated increased signal in response to TF-matched stimuli in left medial Heschl's gyrus (mHG, Table 2, Figure 2A) at the single-voxel level. This hyperactivity in mHG, the likely location of primary auditory cortex (Penhune et al., 1996;Rademacher et al., 2001), was not significant for other stimulus conditions (Figure 2C). Again, mean hearing loss (a "nuisance" covariate in the above analyses) and age did not affect these results; an additional ROI analysis restricted to the four youngest patients yielded hyperactivity for TF-matched stimuli (pSTC: $t_{(13)} = 4.05$, $p = 0.001$; mHG: $t_{(13)} = 3.37$, $p = 0.005$). In addition, hyperactivity in mHG was still apparent when comparing fMRI signal in tinnitus patients on TF-matched trials against fMRI signal in controls on all stimulus trials (ROI analysis, $t_{(20)} = 2.11$, $p = 0.048$). No differences in fMRI signal were seen between groups in any MGN voxels at any stimulus frequency.

Anatomical anomalies in the brains of tinnitus patients

In VBM analyses, significant differences in anatomical images were seen between groups in the subcallosal region, in ventromedial prefrontal cortex (vmPFC; $t > 4.65$ $p < 0.0001$, Figure 3A). For both modulated and unmodulated grey matter (GM) images (interpreted as GM amount and concentration, respectively), tinnitus patients exhibited significantly reduced signal intensity (Figure 3A,B). Tinnitus patients demonstrated a corresponding increase in vmPFC signal intensity in unmodulated white matter (WM) images as well (Figure 3A,B), which can be interpreted as an increase in WM concentration in this region relative to other types of tissue.

These effects appear to be independent of age and total GM or WM volume; these factors were used as covariates in all VBM analyses. Additionally, these between-groups differences persisted when mean hearing loss was entered as a covariate in ROI analyses as well (GM amount: $t = 4.70$, $p < 0.0001$; GM concentration: $t = 5.76$, $p < 0.00001$; WM concentration: $t = 7.14$, $p < 0.00001$). Thus, anatomical differences were not related to measurable hearing loss. Examination of pairwise scatterplots of anatomical effects and age or hearing loss (Figure 3C,D) shows little relationship between group differences in VBM measures and these variables, and additional ROI analyses comparing the youngest patients and control participants yield similar results (GM amount, patients < controls: $t_{(13)} = 4.84$, $p = 0.0003$; GM concentration, patients < controls: $t_{(13)} = 4.68$, $p = 0.0004$; WM concentration, patients > controls: $t_{(13)} = 4.97$, $p = 0.0003$).

In a masked analysis restricted to voxels within auditory-sensory regions, including auditory cortex, MGN, and IC, no significant differences were found between tinnitus patients and controls ($p > 0.01$).

Structure-function correspondence in tinnitus-related regions

In a masked VBM analysis restricted to NAc voxels that demonstrated a significant functional difference between participant groups, there was no significant corresponding anatomical difference ($p > 0.01$). Similarly, in a masked fMRI analysis restricted to vmPFC voxels that demonstrated significant anatomical between-groups differences, we saw no significant functional difference between tinnitus patients and controls ($p > 0.01$). So, no single brain region exhibited both structural and functional differences.

There was, however, a correlation between NAc fMRI signal and vmPFC VBM values in tinnitus patients ($r = 0.73$, $t_{(8)} = 2.99$, $p = 0.02$; outlier removed, see Methods), such that patients with the highest degree of NAc hyperactivity also had correspondingly greater anatomical differences (i.e., decreases in GM concentration and amount, with increased WM amount compared to controls; Figure 4A). This relationship was not present in control participants ($r = -0.03$, $t_{(9)} = -0.10$, $p = 0.919$). Moreover, there was moderate correspondence between limbic abnormalities and primary auditory cortex hyperactivity in tinnitus patients (NAc × mHG: $r = 0.51$, $t_{(8)} = 1.67$, $p = 0.13$, Figure 4B; vmPFC × mHG: $r = 0.61$, $t_{(8)} = 2.17$, $p = 0.06$, Figure 4C). Correlations between limbic and posterior auditory areas were not significant (NAc × pSTC; $r = 0.17$, $t_{(8)} = 0.49$, $p = 0.64$, Figure 4D; vmPFC × pSTC: $r = 0.42$, $t_{(8)} = 1.30$, $p = 0.23$, Figure 4E), nor was activity in primary and posterior auditory cortex related (mHG × pSTC: $r = -0.13$, $t_{(8)} = 0.38$, $p = 0.72$, Figure 4F). This suggests that the degree of functional and structural differences in the limbic system (i.e., NAc and vmPFC, respectively) and primary auditory cortex may be directly related in tinnitus patients.

Discussion

In this paper, we report both functional and structural markers of chronic tinnitus in limbic and auditory regions of the human brain. The most robust of these tinnitus-related differences were located in limbic areas previously shown to evaluate the significance of stimuli (Kable and Glimcher, 2009), including the nucleus accumbens (NAc; part of the ventral striatum) as well as the ventromedial prefrontal cortex (vmPFC). In tinnitus patients, the NAc exhibited hyperactivity specifically for stimuli matched to each patient's tinnitus frequency (i.e., TF-matched). Corresponding anatomical differences were identified in the vmPFC, which is strongly connected to the ventral striatum (Di Martino et al., 2008; Ferry et al., 2000). Indeed, the magnitude of these effects in NAc and vmPFC were related in the current study, suggesting that these regions play a similar role in tinnitus pathology. Within auditory cortex, we noted hyperactivity in mHG, the likely location of primary auditory cortex (Penhune et al., 1996; Rademacher et al., 2001), and posterior superior temporal cortex (pSTC), a secondary auditory region. This increased activity in tinnitus patients was present for all stimuli in pSTC; however, hyperactivity in mHG was restricted to TF-matched stimuli and was positively correlated with tinnitus-related limbic abnormalities as well. Overall, our data suggest that both auditory and limbic regions are involved in tinnitus, and that interactions between the limbic corticostriatal network and primary auditory cortex may be the key to understanding chronic tinnitus.

Limbic system contributions to tinnitus

Many have proposed a role for the limbic system in tinnitus pathology; however, the exact nature of limbic contributions to tinnitus is unknown. We have previously proposed that

chronic tinnitus is caused by a compromised limbic corticostriatal circuit, which results in disordered evaluation of the tinnitus sensation's perceptual relevance and, thus, disordered gain control of the tinnitus percept (Mühlau et al., 2006; Rauschecker et al., 2010). The same corticostriatal network has been implicated in evaluation of reward, emotion, and aversiveness in other domains as well (Bar, 2009; Blood et al., 1999; Breiter et al., 2001; Kable and Glimcher, 2009; Ressler and Mayberg, 2007; Sotres-Bayon and Quirk, 2010). This suggests that the corticostriatal circuit is part of a general "appraisal network," determining which sensations are important, and ultimately affecting how (or whether) those sensations are experienced. In the current study, we provide evidence that these structures, specifically the NAc and vmPFC, do indeed differ in the brains of individuals with tinnitus.

The vmPFC and NAc are part of a canonical cortico-striatal-thalamic circuit, in which vmPFC exerts excitatory influence on the NAc, among other structures (Figure 5) (Divac et al., 1987;Ferry et al., 2000;Jayaraman, 1980). The reductions in vmPFC GM-markers we report are consistent with reduced functional output of vmPFC in tinnitus patients (Schlee et al., 2009). However, although vmPFC markers and NAc hyperactivity are clearly related (Figure 4), the exact nature of this relationship remains to be determined. Increased NAc activity could reflect disinhibition of NAc resulting from decreased vmPFC input to local inhibitory interneurons, though it may also reflect aberrant auditory activity (i.e., tinnitus or TF-matched stimulus) entering the limbic system via the amygdala. Positive correlations between NAc and mHG activity support both hypotheses; future research regarding connectivity between these structures in tinnitus patients are needed to shed light on these issues. Additionally, measuring possible up- or down-regulation of neurotransmitter receptors and/or transporters in these structures could be a target for future studies.

Regardless of its origin, we argue that NAc hyperactivity indicates appraisal of the perceptual relevance of the tinnitus sensation (and/or perhaps the aversiveness of TF-matched stimuli), with the ultimate objective of affecting perception. VmPFC also projects to the thalamic reticular nucleus (TRN), including its auditory division (Zikopoulos and Barbas, 2006), which is in a position to inhibit (or modulate) communication between auditory cortex and MGN (Figure 5). Thus, inefficient vmPFC output could prevent inhibition of the tinnitus signal at the MGN. As such, positive correlation between the magnitude of vmPFC anomalies and NAc/mHG activity may indicate some preservation of function: Those patients with greater amounts/concentrations of GM in vmPFC exhibit less hyperactivity in NAc and mHG, thus reflecting a relatively greater ability of the vmPFC to exert an inhibitory influence on the auditory system.

Auditory system contributions to tinnitus

Tinnitus patients demonstrated increased auditory cortical activation in response to sound in our study. Specifically, medial Heschl's gyrus (mHG) exhibited hyperactivity in response to TF-matched stimuli, and posterior superior temporal cortex (pSTC) was hyperactive across all stimulus frequencies tested.

Most theories regarding tinnitus pathophysiology involve dysfunction of the central auditory system (Eggermont and Roberts, 2004; Jastreboff, 1990; Møller, 2003). However, precise characterization of this process has been complicated by several factors. Potential sites of tinnitus generation are likely to include parts of the auditory pathway that are thought to process relatively simple (i.e., tinnitus-like) stimuli. Thus in our study, sound-evoked hyperactivity in mHG is a likely candidate, given that it typically coincides with primary auditory cortex (Rademacher et al., 2001). However, hyperactivity or dysfunction in one auditory region may merely be a consequence of a tinnitus signal generated elsewhere in the auditory pathway. Indeed, although tinnitus-related dysfunction has been previously identified in primary auditory cortex (Sun et al., 2009), other auditory regions have been

implicated as well (Eggermont and Roberts, 2004; Melcher et al., 2000). Moreover, the location and nature of dysfunction that ultimately generates the chronic tinnitus percept may differ from the site and nature of initial damage, which itself may vary across patients (Henry et al, 2005). Therefore, research concentrating on the exact mechanisms that generate the tinnitus signal within the auditory pathways, whether an increase in baseline activity (Eggermont and Roberts, 2004), reorganization of frequency maps (Eggermont and Komiya, 2000; Irvine et al., 2003; Mühlnickel et al., 1998; Rajan et al., 1993; Weisz et al., 2005; Wienbruch et al., 2006), or some other mechanism, is needed. This is of particular importance given that, although studying stimulus-evoked neural activity is informative, it may not be equivalent to measuring activity corresponding to the tinnitus itself, since sound can have variable effects on patients' tinnitus sensations (Tyler et al., 2008). For these purposes, studying individuals with intermittent tinnitus, or using imaging techniques that are able to measure metabolic activity directly (e.g., PET), may be particularly useful.

Several human imaging studies of tinnitus have reported elevated activity in pSTC in association with the tinnitus sensation itself, when tinnitus loudness was modulated either through administration of lidocaine (Reyes et al., 2002) or by facial movements (a relatively rare tinnitus subtype; Giraud et al., 1999; Lockwood et al., 1998). Though its exact role is debated, posterior auditory cortex is thought to subserve relatively complex auditory functions (Griffiths and Warren, 2002; Rauschecker and Scott, 2009), making it an unlikely first site for the generation of tinnitus sensations. Instead, pSTC hyperactivity could reflect the patients' need to separate the tinnitus signal from the remainder of the acoustic environment. This would be consistent with evidence indicating that posterior auditory cortex is involved in the segregation of multiple auditory signals (i.e., the "cocktail party" problem; Alain et al., 2005; Wilson et al., 2007; Wong et al., 2008). For patients in our study, successful task performance depended upon their ability to separate the tinnitus sensation from auditory stimulation; this was not the case for control participants, who did not experience tinnitus. In fact, one could argue that the separation of multiple acoustic signals is a constant concern for tinnitus patients, and therefore is relevant even for those studies not involving concurrent auditory tasks or stimuli (Giraud et al., 1999; Lockwood et al., 1998; Plewnia et al., 2007; Reyes et al., 2002).

Technical considerations: hearing loss and age

Hearing loss and age did not affect any tinnitus-related neural markers we identified in this study. However, both hearing loss and age have been important topics in the field of tinnitus research. The prevalence of tinnitus increases with age, presumably due to increased incidences of hearing loss (Heller 2003; Eggermont and Roberts 2004). Hearing loss can be interpreted as a correlate of peripheral or central auditory system damage and/or dysfunction, the latter of which is a critical component of all current theories of tinnitus pathophysiology. However, audiometry of even an extended range of frequencies (i.e., > 8 kHz) may not capture all types of auditory system dysfunction (e.g., Weisz et al., 2006). Certainly, controlling for the possible influence of age and audiometrically measurable hearing loss is critical to tinnitus research, as we have attempted to do in our study through careful examination of single subject data and covariate analyses. However, restriction of participant samples along these dimensions is not a preferable solution to this problem. It is likely to be those neural markers that are shared across patients of different ages and hearing profiles that are most indicative of tinnitus pathophysiology, and therefore may be most likely to lead to effective treatments.

Conclusions: Limbic-auditory interactions in tinnitus

In our opinion, the key to understanding tinnitus pathophysiology lies in understanding how the auditory and limbic systems interact. The present study reports, for the first time,

functional differences in the NAc of patients with chronic tinnitus. Furthermore, this hyperactivity in NAc correlates with the magnitude of structural changes in the vmPFC in these same patients. We conclude, therefore, that a dysregulation of limbic and auditory networks may be at the heart of chronic tinnitus. A complete understanding and ultimate cure of tinnitus may depend on a detailed understanding of the nature and basis of this dysregulation. Given the paucity of effective treatments for tinnitus, this field of research is in need of new and testable ideas, and the model we propose will certainly benefit and evolve from future research. For example, although we report moderate correlations between functional activity in primary auditory cortex and limbic regions in tinnitus patients, additional studies are needed to directly assess the nature of connectivity between these and other limbic and auditory regions. We have proposed topographic inhibitory influence of the thalamic reticular nucleus (TRN) on auditory thalamic (i.e., MGN) transmission as a candidate noise-cancellation site in this network (Mühlau et al., 2006; Rauschecker et al., 2010); however, further research is needed to test the site(s) of limbic-auditory interaction relevant for tinnitus, particularly in animal models of tinnitus.

Limbic corticostriatal structures (i.e., vmPFC and NAc) have also been linked to disordered appraisal of hedonic state in drug addiction (Ahmed and Koob, 1998) and emotional state in mood disorders (Mayberg, 1997). Both these conditions are associated with structural abnormalities in vmPFC (Drevets et al., 1997; Koenigs and Grafman, 2009; Tanabe et al., 2009) similar to the ones we report in individuals with chronic tinnitus. Adjacent mPFC and cingulate structures, along with other limbic regions, have also been implicated in chronic pain (DaSilva et al., 2008; Geha et al., 2008; Kuchinad et al., 2007), which too may involve the inability to suppress unwanted sensory signals. Converging evidence regarding common mechanisms shared between these and similar disorders will further our understanding of the limbic system and its influence on perception. Tinnitus, as a relatively circumscribed condition, may facilitate better understanding of limbic dysregulation in many of these disorders.

Methods

Participants

Twenty-two volunteers (11 tinnitus patients, 6 female; 11 controls, 7 female) were recruited from the Georgetown University Medical Center community and gave informed written consent to participate in this study. Tinnitus patients ranged widely in age (20–64 yrs; SD = 16.0 yrs) and were on average 44.4 years old; the mean age of control participants was 23.0 years (SD = 3.3, Table 1). Participants reported no history of neurological disorders, though one tinnitus patient reported a diagnosis of clinical depression at the time of the study, for which he was taking antidepressants. Data collected from this participant did not differ appreciably from that of other patients; this participant's data have been noted when possible in Tables and Figures. No other participants reported a history of mood disorders.

Patients reported having chronic tinnitus, which we defined as being present either constantly or intermittently for at least 6 months (mean = 9.7 years, SD = 17.6 years). Self-reported severity of tinnitus impact was measured on a scale roughly comparable to the Tinnitus Handicap Inventory (THI) (Newman et al., 1996). Its outcome varied across patients, but was generally mild-to-moderate (Suppl. Table 2). Patients reported no history of severe hyperacusis or phonophobia, and in a short survey reported limited or no sensitivity to noise (Suppl. Table 2). Neither tinnitus severity nor noise sensitivity scores correlated with the magnitude of neural tinnitus-markers we report (data not shown), and are therefore not discussed here.

Audiological examination

All participants underwent audiological testing to determine hearing levels. Pure tones ranging from 250 Hz to 12 kHz were presented to each ear until the threshold of detection was reached. Two control participants were tested at a more conventional range of frequencies (250 Hz to 8 kHz in octave steps). Using a relatively strict classification scheme, all but three participants (two controls and one tinnitus patient) exhibited some degree of hearing loss at one or more of the tested frequencies (Suppl. Figure 1). Eleven participants (4 tinnitus patients) exhibited a mild or moderate hearing loss at one or more frequencies (20–40 dB or 40–60 dB above threshold, respectively), and eight participants (6 tinnitus patients) demonstrated severe loss in at least one tested frequency (60–90 dB above threshold). No participants showed profound hearing loss at any frequency (> 90 dB above threshold).

Tinnitus patients underwent additional audiological testing to find the best match to the perceived frequency of their tinnitus. Patients initially identified the pure tone from the audiological examination that best matched the center frequency of their tinnitus sensation. Then, subsequent pure tones were presented in neighboring frequencies until a match was identified. All patients reported having a tinnitus sensation with a clearly definable pitch. Tinnitus frequencies ranged from 150 Hz to 12 kHz (Table 1), but were generally high (mean = 6,083 Hz, SD = 4,100 Hz).

Stimulus construction and presentation

Stimuli consisted of band-passed white noise (BPN) bursts with 0.167 octave bandwidth, and were presented in trains at 3 Hz for 6 s per trial. BPN center frequencies were dependent on the best match of the tinnitus frequency of each patient; they were either matched to the tinnitus frequency, or were 0.5, 1, or 2 octaves above or below the tinnitus frequency. To ensure that stimuli remained within normal hearing range (i.e., below 20 kHz, Suppl Table 1), center frequencies were adjusted in some cases to accommodate instances of high-frequency tinnitus sensations. For each tinnitus patient, a “stimulus-matched” control participant completed the experiment with the same range of stimulus frequencies.

During scans, stimuli were presented via in-ear electrostatic headphones (*Stax*), constructed to have a relatively flat frequency response up to 20 kHz (±4 dB). Stimuli were first adjusted to a comfortable volume determined by the subject in the scanner environment (~60–65 dB SPL), with attenuation of ambient noise provided by ear defenders (~26 dB SPL reduction, *Bilsom*). Then, stimulus level was adjusted in a stimulus-specific manner to reflect each participant’s detection threshold at each frequency in the scanner. These adjustments were not made for two tinnitus patients and their stimulus-matched controls.

Participants were asked to perform an “oddball” task during the fMRI experiment. On 8% of trials, BPN stimulus trains were interrupted by a short period of silence. On these target trials, participants were instructed to respond via button press. On nontarget trials, participants were not to make any response. Data associated with less than 80% accuracy on this task were excluded from further analysis. Eighteen participants (9 patients) completed this task; the remaining four (2 patients) were asked to listen attentively to intact BPN stimulus trains and make no response.

Image acquisition and processing

Images were acquired using a 3.0 Tesla Siemens Trio scanner. Two sets of functional echo-planar images (EPI) were acquired using a sparse-sampling paradigm: repetition time (TR) = 10 s, TR delay = 7.72 ms, echo time (TE) = 36 ms, flip angle = 90°, 25 axial slices, 1.5 × 1.5 × 1.9 mm^3 resolution. A high-resolution anatomical scan (MPRAGE) was also performed

for each subject: TR = 2,300 ms, TE = 2.94 ms, inversion time (TI) = 900 ms, flip angle = 9°, 160 sagittal slices, matrix size 256 × 256 mm^2, 1 × 1 × 1 mm^3 resolution. Data for four participants (2 patients) were acquired using nearly identical sequences with the following differences: EPI, TR = 12 s, TR delay = 9.72 ms; MPRAGE, TR = 1600 ms, TE = 4.38 ms, TI = 640 ms, flip angle 15°. The field of view of functional EPI images was restricted to auditory cortex, subcortical structures superior to the midbrain (i.e., including MGN but not inferior colliculi), and ventral prefrontal cortex. A standard field of view encompassing the entire brain was used for anatomical images.

Functional imaging analyses were completed using BrainVoyager QX *(Brain Innovation, Inc)*. Functional images from each run were corrected for motion in six directions, relieved of linear trend, high-pass filtered at 3 Hz, and spatially smoothed using a 6-mm full-width-at-half-maximum (FWHM) Gaussian filter. Data were then coregistered with anatomical images, and interpolated into Talairach space (Talairach and Tournoux, 1988) at 3 × 3 × 3 mm^3 resolution.

Voxel-based morphometry (VBM) analyses were completed using SPM8 *(Wellcome Trust Centre for Neuroimaging)*. Anatomical images were corrected for intensity bias, spatially normalized, and segmented into white matter, grey matter, and cerebrospinal fluid using tissue probability maps (*International Consortium for Brain Mapping*). Grey and white matter images were then modulated to reflect the degree of local deformation applied during spatial normalization, and smoothed using a 12-mm FWHM Gaussian filter. All images were thresholded at 0.20 probability of tissue classification. This yielded four types of anatomical images for use in subsequent VBM analyses: unmodulated grey, unmodulated white, modulated grey, and modulated white matter images. Umodulated images are thought to reflect the concentration (or “density”) of a tissue class relative to other tissues, while data from modulated images are argued to reflect the amount (or “volume”) of a particular tissue class in a given anatomical area (Ashburner and Friston, 2000).

Interpretation of voxel-based morphometry (VBM) results is not always straightforward. Ashburner and Friston (2000) explain that unmodulated, segmented images (i.e., images not adjusted to reflect the degree of warping during spatial normalization) reflect the concentration of a tissue type in a given area relative to other tissue types. This is often referred to as tissue “density”. Thus, values along tissue borders are complementary as they are blurred during smoothing, which may partially explain, e.g., corresponding decreases in GM concentration and increases in WM concentration within a single area. Note also that VBM concentrations (unmodulated values) have not been directly linked to cellular make-up or density thus far. VBM values adjusted for the degree of deformation applied during spatial normalization (i.e., modulated values) reflect the total amount of a tissue type in a given region (Ashburner and Friston, 2000). Although these modulated values are often interpreted as a proxy for “volume,” direct measurements (e.g., of cortical thickness) would be necessary to confirm volumetric differences in a given region.

Statistical analyses

Functional images—Group analyses using the general linear model (GLM) were executed in single voxels and in regions of interest (ROIs), in order to assess the relationship between fMRI signal and our experimental manipulations (i.e., regressors; Friston et al., 1995) using BrainVoyager. Trials were binned based on their relationship to the tinnitus frequency (TF) into trials in which: 1) BPN center frequency (BPNCF) was more than 0.5 octaves below TF, 2) BPN_{CF} was less than or equal to 0.5 octaves below TF, 3) BPN_{CF} matched TF, 4) BPN_{CF} was less than or equal to 0.5 octaves above TF, and 5) BPN_{CF} was more than 0.5 octaves above TF. These five stimulus conditions were entered as GLM regressors, along with “confound” regressors corresponding to task oddball trials and subject

identity (to reduce the influence of inter-subject variability). Single-subject beta maps were generated for each of five stimulus conditions, which were then used to assess between-group differences in function using Analyses of Covariance (ANCOVAs). Participant group (i.e., tinnitus patients vs. controls) and mean hearing loss (mHL) were entered as a between-subjects factor and covariate, respectively. Single-voxel thresholds were chosen ($p < 0.001$); maps were then corrected for cluster volume at $p_{(corr)} < 0.05$ using Montecarlo simulations (a means of estimating the rate of false positive voxels; Forman et al., 1995). Single-voxel thresholds were reduced to $p_{(uncorr)} < 0.01$, $k > 108$ mm^3 in masked analyses (below).

Anatomical images—Single-voxel GLM analyses assessed anatomical differences between tinnitus patients and controls, with compensation for unequal variance between groups in SPM8. T-tests were performed across groups, and both age and total grey or white matter volume were entered as confound covariates. A single-voxel (i.e., voxel-wise) threshold was chosen of $t > 4.65$, $p < 0.0001$; cluster volume was greater than 80 mm^3. Single-voxel thresholds were reduced to $p < 0.01$ in masked analyses. All single-voxel VBM analyses were performed in the same resolution as the tissue probability maps used for segmentation ($2 \times 2 \times 2$ mm^3).

Mask and ROI creation—A mask of the auditory system was created for both functional and anatomical analyses. Auditory cortex was defined by selecting those functional voxels in superior temporal cortex that survived a sounds > silence contrast with a single-voxel threshold of $t > 2.58$, $p_{(uncorr)} < 0.01$, $k > 4$ (group data). The MGN were defined using the WFU Pick Atlas (Lancaster et al., 2000; Maldjian et al., 2003), dilated by 1 mm, and then flipped to create a symmetrical mask in both hemispheres. Additional masks were created using significant clusters from both functional and anatomical analyses. Masks were transferred between programs via image files (ANALYZE format), which were then adjusted to the appropriate format in BrainVoyager or SPM. Coordinate conversions between Talairach and MNI spaces were done using a well-accepted nonlinear transform (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach).

Correlation analyses—Pairwise correlations between mean fMRI signal or VBM values were performed for ROIs exhibiting significant between-groups differences using the statistical tests described above. Cook's d tests were used to assess the influence of potential outliers on the resulting correlation statistics. Data points from a single participant, Patient #7, had Cook's d values close to 1.0 (a commonly used benchmark for identifying potential outliers) for 4 out of 6 pairwise tests (Suppl. Table 3). Therefore, we computed correlations both with and without this subject included. Excluding this potential outlier significantly affected only one pairwise correlation (Figure 4C), and strengthened other correlations already apparent when including this outlier (Figure 4A,B).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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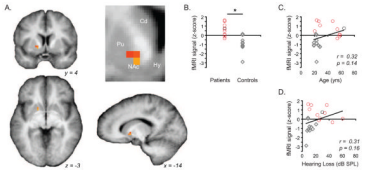

Figure 1.

Hyperactivity in tinnitus patients was localized to the ventral striatum near the nucleus accumbens (center of gravity: X,Y,Z = −16, 6, −0.5; volume = 108 mm^3). **A.** Voxels exhibiting significant ($p_{(corr)} < 0.05$) between-groups differences in fMRI signal are shown on group-averaged anatomical images. Inset in A shows a close-up of the coronal image, emphasizing the position of the cluster in the ventral striatum (nucleus accumbens, NAc; caudate, Cd; putamen, Pu; hypothalamus, Hy). **B–D.** Mean fMRI signal for each subject is plotted for tinnitus patients (red circles) and stimulus-matched control participants (grey diamonds) in **B.** A black circle marks the tinnitus patient reporting comorbid depression; color scheme is constant throughout. Asterisk denotes statistical significance at the single-voxel level demonstrated in A. This functional difference in NAc is not related to participant age (**C**) or mean hearing loss (**D**). Note that where tinnitus patients overlap with control participants in age and mean hearing loss, NAc response still exhibits a clear between-groups difference.

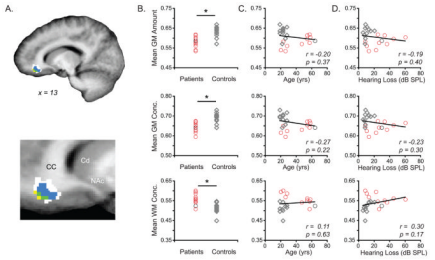

Figure 2.

In a masked analysis restricted to auditory cortex and thalamus, hyperactivity in tinnitus patients was demonstrated in auditory cortex. **A.** Voxels that demonstrated between-groups differences in fMRI signal ($p < 0.01$, $k > 108$ mm^3) are shown on group-averaged anatomical images, rotated to visualize the superior temporal plane (STP). Tinnitus-related hyperactivity was seen during trials containing TF-matched stimuli (yellow), stimuli less than 0.5 octaves below the TF (green), less than 0.5 octaves above the TF (orange), and more than 0.5 octaves above the TF (pink). Blue marks a single instance where signal was less for tinnitus patients. **B–C.** Mean fMRI signal is plotted for tinnitus patients (red) and control participants (grey) for TF-matched stimuli and other stimuli in pSTC (**B**) and mHG (**C**). Brain activity in patients during TF-matched trials was also significantly greater than control participants' during non-TF-matched trials in these regions (pSTC: $t_{(20)} = 4.09$, $p = 0.0003$; mHG: $t_{(20)} = 1.68$, $p = 0.05$; one-tailed tests).

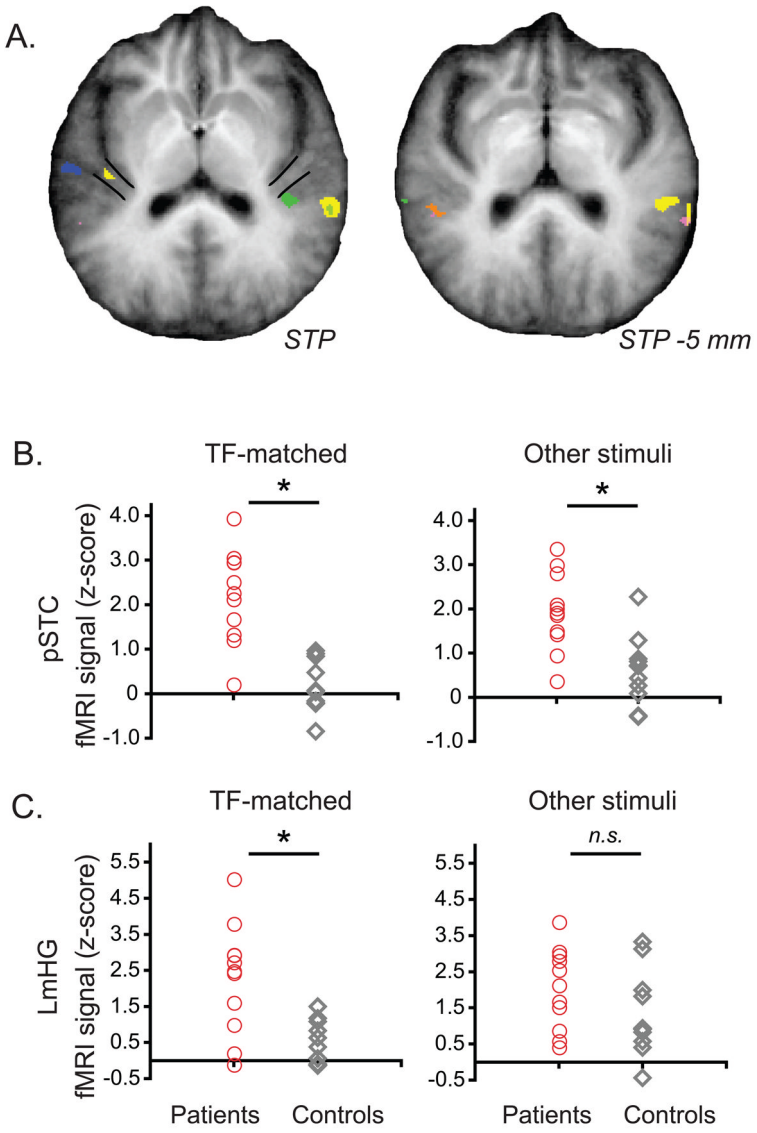

Figure 3.

Structural differences between tinnitus patients and control participants were identified in ventromedial prefrontal cortex (vmPFC). **A.** Voxels demonstrating significant differences in VBM values between groups are shown on group-averaged anatomical images. Inset in A is a close-up of the sagittal image, showing the position of anatomical differences located in vmPFC inferior to the corpus callosum (CC). The position of basal ganglia structures is also indicated (caudate, CD; nucleus accumbens, NAc). Between-groups differences were seen in modulated and unmodulated grey matter (GMm and GMum, respectively) and modulated white matter (WMm) images. White corresponds to WMm differences, yellow marks GMm and WMm differences, blue marks GMum and WMm differences, and green marks differences in GMm, GMum, and WMm. **B–C**. Mean VBM values are plotted for each tinnitus patient (red circles) and control (grey diamonds). Asterisks in B denote the statistically significant differences in GMm (amount, top), GMum (concentration, middle), and WMm (amount, bottom) at the single-voxel level shown in A. These differences were not related to age (**C**) or mean hearing loss (**D**).

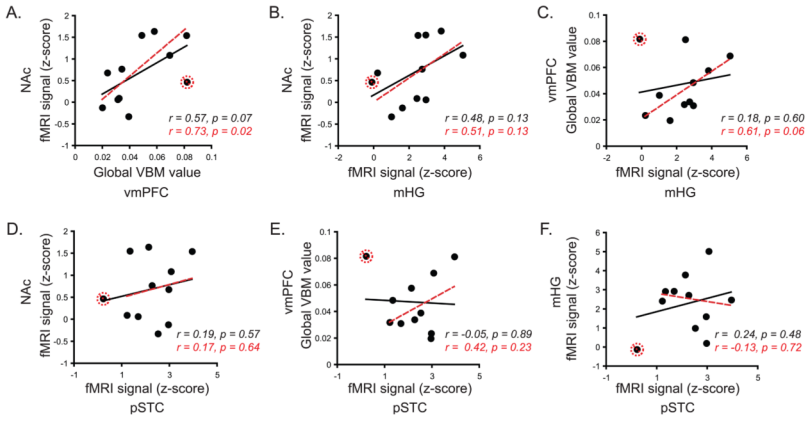

Figure 4.

Correlations between functional and anatomical markers are displayed. Data corresponding to NAc, mHG, and pSTC reflect fMRI signal during TF-matched trials. Global VBM values in vmPFC reflect the mean difference in modulated and unmodulated grey matter and modulated white matter from the corresponding mean values in control participants. Thus, large global VBM values indicate larger difference from controls, while smaller values indicate smaller tinnitus-related differences. A single outlier (see Methods) is marked in red; r and p values are displayed for each pairwise correlation both including (black) and excluding (red) this outlier.

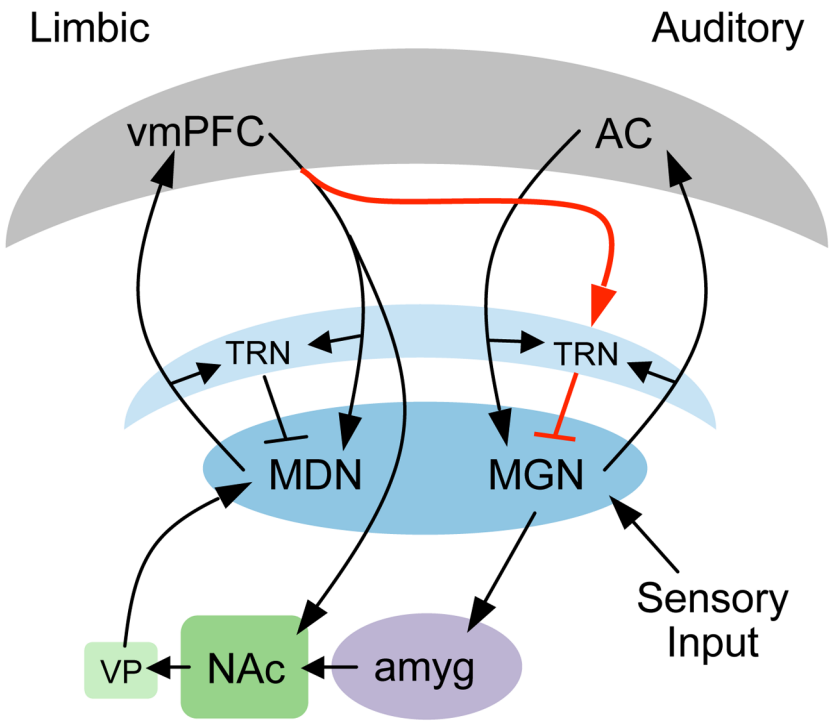

Figure 5.

Schematic of proposed auditory-limbic interactions in tinnitus. Sensory input originates subcortically and enters both auditory and limbic circuits via the medial geniculate nucleus (MGN). Under normal circumstances, the limbic system may identify a sensory signal as perceptually irrelevant (e.g., transient tinnitus following loud noise exposure), and inhibit the unwanted signal at the MGN via projections from the ventromedial prefrontal cortex (vmPFC) to the auditory thalamic reticular nucleus (TRN, red pathway). Thus, propagation of the unwanted signal (e.g., transient tinnitus) is reduced in both circuits. In chronic tinnitus, inefficient vmPFC output prevents inhibition of the tinnitus signal, resulting in continued thalamocortical activity and the constant perceptual presence of the tinnitus signal. Cortical structures are noted in grey, thalamus is noted in blue, basal ganglia in green, and amygdala in lavender. Schematic is not to scale, and position of structures was not made to accurately reflect anatomical position. Abbreviations: medial dorsal nucleus (MDN), ventral pallidum (VP), amygdala (amyg), auditory cortex (AC).

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Table 1

Participant characteristics

Participant	Sex	Age (years)	HL, mean (dB SPL)	HL, SD (dB SPL)	TF (Hz)	Tinnitus Ear
Patient #1	m	64	29.66	26.01	1,200	right
Patient #2	m	57	26.18	19.66	8,000	bilateral
Patient #3	f	26	13.05	12.31	6,666	bilateral
Patient #4	m	23	8.34	7.60	9,000	right
Patient #5	m	47	36.34	21.96	8,000	bilateral
Patient #6	f	58	60.26	21.24	150	bilateral
Patient #7	f	20	22.24	8.83	3,334	bilateral
Patient #8	f	54	33.34	18.74	10,666	left
Patient #9	f	54	44.89	27.72	9,333	bilateral
Patient #10	f	28	10.32	4.97	6,666	bilateral
Patient #11	m	57	24.58	13.98	12,000	right
Control #1	f	22	8.33	1.29	*1,200*	*n/a*
Control #2	f	26	8.75	5.65	*8,000*	*n/a*
Control #3	m	23	8.45	6.23	*6,666*	*n/a*
Control #4	m	28	10.95	9.23	*9,000*	*n/a*
Control #5	m	23	5.71	4.07	*8,000*	*n/a*
Control #6	f	23	20.50	12.93	*150*	*n/a*
Control #7	f	19	8.95	4.84	*3,334*	*n/a*
Control #8	f	23	13.29	16.70	*10,666*	*n/a*
Control #9	f	19	15.50	7.81	*9,333*	*n/a*
Control #10	f	19	10.58	8.70	*6,666*	*n/a*
Control #11	m	28	7.13	5.27	*12,000*	*n/a*

Abbreviations: hearing loss (HL), tinnitus frequency (TF). TF numbers in italics indicate stimulus-matching in control participants, not TF.

Table 2

Masked fMRI analysis of auditory cortex and MGN

Contrast	Stimulus	Brain region	X	Y	Z	Volume (mm^3)
patients > controls	TF	L medial Heschl's gyrus	−42	−20	10	162
		posterior temporal plane	46	−28	22	162
		posterior temporal gyrus and sulcus	57	−38	16	1,593
		posterior temporal sulcus	57	−40	8.5	108
			−65	−30	5.2	135
	TF++	posterior temporal plane	−52	−40	15	135
		posterior temporal gyrus	62	−43	18	135
	TF+	posterior temporal plane	−49	−38	12	108
	TF−	posterior temporal plane	58	−33	22	135
			39	−31	19	270
controls > patients	TF+	mid superior temporal sulcus	−50	−29	−0.2	135
	TF−	mid superior temporal plane	−56	−19	7.3	297

Abbreviations: tinnitus frequency (TF), stimuli more than 0.5 octaves above TF (TF++); stimuli less than 0.5 octaves above TF (TF+); stimuli less than 0.5 oct below TF (TF−); stimuli lower than 0.5 oct below TF (TF−−).