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Functional Connectivity Networks in Nonbothersome Tinnitus

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Abstract

Objective—To assess functional connectivity in cortical networks in patients with nonbothersome tinnitus compared with a normal healthy nontinnitus control group by measuring low-frequency (<0.1 Hz) spontaneous blood oxygenation level–dependent (BOLD) signals at rest.

Design—Case-control.

Setting—Academic medical center.

Participants—Nonbothersome, idiopathic subjective tinnitus for at least 6 months (n = 18) and a normal healthy nontinnitus control group (n = 23).

Main Outcome Measure—Functional connectivity differences in 58 a priori selected seed regions of interest encompassing cortical loci in the default mode, attention, auditory, visual, somatosensory, and cognitive networks.

Results—The median age of the 18 subjects was 54 years (interquartile range [IQR], 52–57), 66% were male, 90% were white, median Tinnitus Handicap Inventory (THI) score was 8 (IQR, 4–14), and a median Beck Depression Index score was 1 (IQR, 0–5). The median age for the control group was 46 years (IQR, 39–54), and 52% were male. Of the 58 seeds analyzed, no regions had significantly different functional connectivity among the nonbothersome tinnitus group when compared with the control group.

Conclusion—Among nonbothersome tinnitus patients, the tinnitus percept does not appear to alter the functional connectivity of the auditory cortex or other key cortical regions.

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Keywords

tinnitus; functional; imaging; rest; connectivity; fc-MRI; resting fMRI; human

Tinnitus is more than ringing in the ear; it is associated with a variety of nonauditory symptoms that include difficulty concentrating, inability to relax, frustration, and depression.[1–4] However, this may represent only a small fraction of the actual tinnitus population. According to the American Tinnitus Association, tinnitus affects nearly 50 million Americans, yet only one-third will seek medical therapy because they are bothered. Although some investigators hypothesize tinnitus patients become "bothered" either by a lack of habituation[5] or abnormal limbic activity,[6–8] no study has focused on patients with nonbothersome tinnitus. These patients lack the cognitive and emotional sequelae commonly seen with bothersome tinnitus and can serve as a better cohort to understand the underlying neurobiology of tinnitus.

Neuroimaging provides a noninvasive approach to studying tinnitus. Early studies captured blood flow changes in frontal, parietal, and temporal areas via positron emission tomography (PET) with lidocaine injection,[9–12] behavioral task,[13] and tinnitus modulating behaviors.[6,14] Using radioactive glucose in PET allowed visualization of asymmetrical increased metabolic activity of the auditory cortex.[15–18] However, a major shortcoming of PET is the poor spatial resolution and radiation exposure. Even though magnetic resolution imaging (MRI) is associated with significant scanner noise, MRI has gained increasing popularity in studying tinnitus as it is cheaper, quicker, and provides better resolution without harmful radiation when compared with PET. Functional MRI (fMRI) measures cerebral blood flow based on the blood oxygen level–dependent (BOLD) signal.[19] The BOLD signal acts as an in vivo contrast agent; brain regions with increased neural activity use the faster anaerobic glycolysis,[20] resulting in proportionally *increased* amounts of oxyhemoglobin (ie, the BOLD signal). In tinnitus studies, an auditory stimulus is sent to the participant through headphones; the activity before and after the stimulus is then compared. A major limitation in task-based fMRI is that participants need to be able to perform task(s) or, in the case of tinnitus, hear the stimulus. A relatively underused technique in studying tinnitus using MRI involves measuring the spontaneous BOLD signal while the participant is at rest. Small fluctuations in the spontaneous BOLD activity below 0.1 Hz, originally considered to be "noise," are significantly correlated across engaged brain networks. In 1995, Biswal et al[21] found significant resting state temporal correlations within the somatomotor network. Subsequent functional connectivity analyses of spontaneous activity (fcMRI) revealed dorsal and ventral attention,[22] cognitive control,[23] auditory,[24] visual,[24,25] somatomotor,[22] and default mode networks.[21,24,26,27]

In our previous work, we used fcMRI to study resting state activity within a cohort of participants with bothersome tinnitus compared with a cohort of controls without tinnitus. We found alterations in sensory and cognitive control networks.[28] In this study of nonbothersome tinnitus, we hypothesize that there will be *no differences* in functional connectivity when compared with the control group used in our bothersome tinnitus study.

This "sister study" duplicates the methodology of our previous study with regard to controls used, analytical methods, and seeds of interest analyzed.

Materials and Methods

Design and Setting

This was a single-institution (Washington University), case-control study to examine differences in functional connectivity in a nonbothersome tinnitus (NBT) group compared with a normal-hearing, healthy control group without tinnitus. The institutional review board provided approval prior to recruitment.

Participants

Adult participants were enrolled from October 2010 to April 2011 and were recruited from (Washington University) audiology or otolaryngology clinics. Of the 20 recruited participants, 2 were excluded from analysis due to excessive head motion. The remaining 18 participants had nonpulsatile subjective tinnitus, unilateral (n = 6) or bilateral (n = 12), for at least 6 months. Exclusion criteria included anyone with (1) an active diagnosis of any acute or chronic brain-related neurological conditions; (2) history of head trauma, seizure, or stroke; (3) a retrocochlear lesion or anatomic/structural lesion of the brain, skull base, temporal bone, or ear; or (4) active depression or anxiety disorder or who had recently began taking medications to treat depression or anxiety. Participants completed the following American Tinnitus Association data collection forms: (1) tinnitus description and history, (2) medical and health information, and (3) hearing history and occupation exposure. Participants also completed the Beck Depression Inventory-II (BDI-II)[29] to evaluate level of depression. All tinnitus participants had a recent (<12-month) audiogram and underwent a focused ear, nose, and throat physical examination.

Resting State Functional Connectivity MRI

The resting state functional connectivity MRI (rs-fcMRI) data were obtained and processed as previously described.[28]

Image acquisition—All images were collected on a Siemens 3 T Trio scanner (Erlangen, Germany) while participants wore noise-reducing headphones. Three 164-frame echo-planar sequence (EPI) runs recorded spontaneous brain activity while participants were awake, performed no task, and kept their eyes closed in a darkened room. Structural images included both a T1-weighted magnetization-prepared rapid gradient echo sequence acquired across 176 sagittal slices and a T2-weighted structural image obtained across 36 axial slices.

Image preprocessing and computing functional connectivity maps—Preprocessing involved compensation for head motion, asynchronous slice acquisition, band-pass filtering to remove nuisance variables, and whole-brain signal normalization to mode 1000. Slices were resampled to 2-mm^3 volumes (voxels) and registered to an atlas template by computing 12 parameter affine transforms between an average from the first frames of each EPI run and the atlas template.[30] Using MP-RAGE images, an atlas template was created and conformed to Talairach atlas space.[31] Fifty-eight spherical seed regions

were chosen to represent established networks.[21–27] An initial screening of possible group differences relied on computed temporal correlations between every pair of seed regions in each participant. The time series included 17.5 minutes of spontaneous activity and was averaged across all voxels. In the first stage of analysis, all correlations were transformed into *z* scores using Fisher's transformation; a *t* test, not corrected for multiple comparisons, evaluated group differences. In a second-stage analysis, we computed functional connectivity maps in each participant for seed regions whose paired temporal correlations had group differences with probabilities <0.01, as shown in Figure 1. The computed correlations were between the time series averaged across all voxels in a seed region and the time series in each 2-mm cubic volume in the brain.[27] These voxel-based correlation values were then registered to participant-specific cortical surfaces using FreeSurfer (Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, Massachusetts) and then deformed to the PALS-B12 atlas.[32] Next, we computed a *t* statistic at each surface node to assess the null hypothesis that the Fisher's transform *z* scores for a seed region were comparable between the control and NBT groups. The *t* statistic was computed as the mean difference (control group *z* transform score minus NBT group z transform score) divided by the SEM difference. Significant clusters appear if they reach probability thresholds of 0.05 to 0.001 ($t = \pm 1.7$ and 3.3 for 39 *df*). We assessed the significance of clusters observed in the group contrast *t* statistic maps with a threshold-free cluster enhancement (TFCE) method. Clusters in the original *t* statistic map were judged significant at $P = .05$.

Results

Participants

The median age of the NBT group (n = 18) was 54 years (interquartile range [IQR], 52–57), 66% were male, median Tinnitus Handicap Inventory (THI) score was 8 (IQR, 4–14), and a median BDI-II score was 1 (IQR, 0–5). A THI <16 characterizes the least severe tinnitus grade,[33] and a BDI-II <14 is considered minimally depressed.[34] Table 1 presents audiogram findings for each tinnitus participant. Overall, the group had a wide range of hearing loss from mild to severe. The median duration of tinnitus was 9 years and perceived loudness of 5 on a scale from 1 (low) to 10 (high). Study subjects reported a wide variety of sounds (Table 2).

The control group was composed of 23 individuals who served as healthy controls in our previous bothersome tinnitus study. The median age for the control group was 46 years (IQR, 39–54), and 52% were male. The control group had pure-tone average thresholds of <25 dB.

With respect to the control group, the NBT group was significantly older (Δ 8 years; 95% confidence interval [CI], 3.1–12.9, $P = .002$) but did not significantly differ in gender (Δ 14%, $\chi^2 = 0.874$, $df = 1$, $P = .35$).

Temporal Correlation Matrix and Functional Connectivity

An initial screening of possible group differences relied on computed temporal correlations between every pair of seed regions in each participant. In the first stage of analysis, all

correlations were transformed into *z* scores using Fisher's transformation and a *t* test evaluated group differences. Fifteen significant *t* tests ($P < .01$) shown in Figure 1 reflect the first stage of analysis. Only these significant seeds continued on to the permutation step, which included family-wide error corrections.[35] None of the 15 significant seed regions from the temporal correlation were significant after the threshold-free cluster enhancement permutation analysis. Figure 2 depicts the control and NBT groups' functional connectivity maps of the left auditory cortex seed and a *t* test illustrating the non-significant difference between the 2 groups.

Discussion

The current study examined functional connectivity in patients who often do not seek medical care because they are not bothered by their tinnitus. Using a seed-based approach, we examined 58 regions representative of established networks.[21–27] When compared with a control group, there were no differences in connectivity. In contrast to our findings in a cohort with bothersome tinnitus,[28] this negative finding indicates that less severe, nonbothersome tinnitus is not associated with abnormal cortical activity.

Prior imaging[6,9,17,36,37] and behavioral[38–41] studies commonly capture tinnitus severity but do not fully appreciate the wide variation of tinnitus severity. For example, the study population in Rossiter et al[41] had a mean (SD) Tinnitus Reaction Questionnaire[3] (TRQ) score of 36 (22), indicating moderate tinnitus severity, but a TRQ range of 0 to 74. This range spanned from those with bothersome tinnitus (TRQ of 74) to those with nonbothersome tinnitus (TRQ of 0). Consequently, it is unclear how to interpret the results of this study that found slower reaction times and poorer accuracy in a dual-task setting when compared with controls. In light of our recent findings, we propose that the findings by Rossiter et al would be even more robust in a more homogeneous cohort (ie, severe tinnitus). Inconsistent tinnitus findings in neuroimaging and behavioral studies may reflect the incorporation of highly variable tinnitus severities into these studies.

Origin of the “bother” in tinnitus

Andersson and McKenna[42] proposed that tinnitus becomes annoying when it interferes with thinking and is more likely to become a problem in those who have an overall anxious or pessimistic outlook on life. This model highlights the heterogeneity of clinical complaints that range from difficulty in concentration to insomnia. Supportive of this model is our identification of significant functional cortical network connectivity differences among bothered (ie, annoyed) tinnitus patients[28] that were not replicated in the nonbothersome tinnitus cohort.

Finding cortical network disruptions among bothered tinnitus patients may indicate a failed attempt of adaption or habituation toward the auditory percept. In the bothered tinnitus cohort,[28] we found altered activity within the ventral attention network (VAN), which is important for involuntarily reorienting to salient stimuli.[43,44] Disruptions of the VAN may explain the difficulty these patients have with responding or reorienting to unexpected stimuli, such as missing a phone call while in deep concentration (ie, a dual-task scenario as in Rossiter et al[41]). The dorsal attention network (DAN) is important for voluntarily shifting

attention.[43,44] Components of the DAN were not affected in our bothersome tinnitus study.[28] An intact DAN explains why people with tinnitus can briefly "control" their tinnitus long enough to perform a specific task but often do poorly in dual-task situations in which they are required to maintain or shift attention.[38,41] Difficulty in shifting attention in the bothered tinnitus group is supported by the disruption of the salience network (ie, frontoinsular network). The salience network helps maintain and adjust attention and has been proposed as a key component in tinnitus reaching consciousness by other researchers.[45] Together, these functional connectivity findings support the model of annoyance proposed by Andersson and McKenna.[42]

Limitations

There are several limitations to our work. First, we only analyzed cortical activity between the 2 groups and did not explore deep brain or brainstem activity. In animal models, changes in activity of the dorsal[46] or ventral[47] cochlear nucleus have been proposed to play a role in tinnitus. There is also evidence from fMRI studies that tinnitus may originate in the inferior colliculus[36,37,48] and cerebellum[49] or arise from hyperactivity within the dorsal and ventral cochlear nucli.[50,51] In addition, our analysis, based on a threshold-free cluster enhancement permutation technique,[35] is very powerful but prone to type II (false-negative) errors. Consequently, this permutation analysis may be unable to detect small functional connectivity cluster differences between 2 groups. However, we published an fcMRI study of patients with bothersome tinnitus[28] using similar methodology and found several dissociations not seen in the current study. The fact that differences were found in the bothersome cohort suggests our methodology is robust.

Conclusions and future directions

This analysis of resting state fcMRI found that patients with nonbothersome tinnitus do not exhibit a global cortical disorganization as seen in our previous study of bothered tinnitus patients. These complementary neuroimaging findings support a model of tinnitus wherein the level of annoyance relates to neurobiological changes as proposed by Andersson and McKenna.[42] The current negative finding in patients with nonbothersome tinnitus and our previous findings in patients with bothersome tinnitus highlight the heterogeneity of this condition. Together these studies emphasize the need to incorporate techniques to identify unique subgroups of tinnitus patients based on the severity of the cognitive and emotional impairments, which we believe reflect the underlying neurobiology of this condition. Imaging, neurocognitive, or intervention studies in humans that recognize the heterogeneity of functional, cognitive, and emotional complaints in tinnitus are more likely to be informative than studies that ignore heterogeneity.

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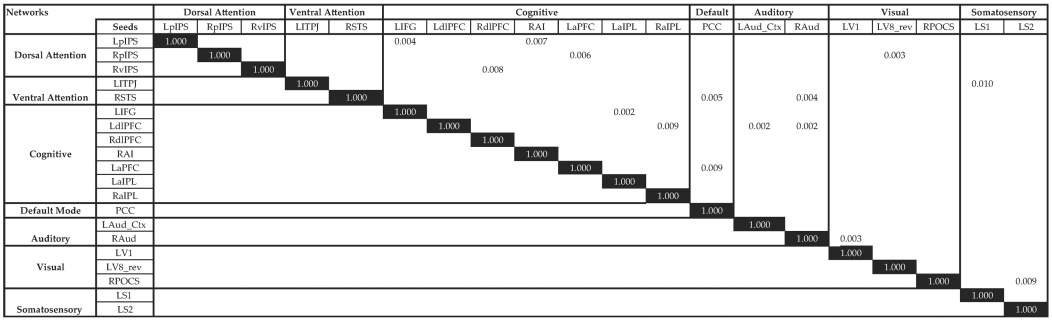

Figure 1.

Significant *t* test probabilities for the differences in connectivity within different seed regions between tinnitus and nontinnitus control groups. Black rectangles represent same-seed comparisons. Abbreviations for significant regions: LaIPL, left anterior inferior parietal lobule; LaPFC, left anterior prefrontal cortex; LAud_Ctx, left auditory cortex; LdlPFC, left dorsolateral prefrontal cortex; LIFG, left inferior frontal gyrus; LpIPS, left posterior intraparietal sulcus; LS1, left postcentral gyrus; LS2, left parietal operculum; LTPJ, left temporoparietal junction; LV1, left calcarine sulcal cortex; LV8, left fusiform gyrus; PCC, posterior cingulate cortex; RAI, right anterior insula; RaIPL, right anterior inferior parietal lobule; RAud, right auditory cortex; RdlPFC, right dorsolateral prefrontal cortex; RpIPS, right posterior intraparietal sulcus; RPOCS, right parieto-occipital sulcus; RSTS, right superior temporal sulcus; RvIPS, right ventral intraparietal sulcus.

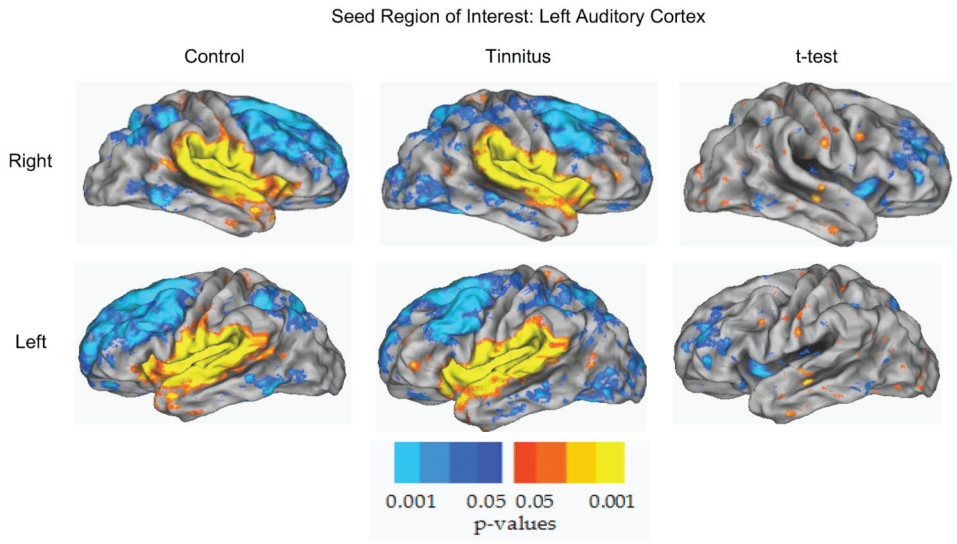

Figure 2.

Functional connectivity map for the left auditory cortex (LAud_Ctx) for the control and tinnitus groups. Functional connectivity for controls (column 1), tinnitus (column 2), and the difference between controls and tinnitus (column 3) displayed on a PALS-B12 atlas surface. The right hemisphere view (row 1), left hemisphere view (row 2), and auditory cortex seed region (black circle) are shown. The distribution of significant positive and negative correlations between time courses in the seed vs other brain regions is shown in shades of blue to yellow. The Difference column represents the difference in activity between controls and tinnitus based on Fisher *z* transforms of correlations. No significant clusters were identified using the left auditory cortex seed region.

Table 1

Audiogram Findings for 18 Participants with Nonbothersome Tinnitus

		500 Hz		1 kHz		2 kHz		4 kHz		8 kHz		
Gender	**Age, y**	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**	**SRT in Worst Ear (Location)**
M	47	15	10	15	15	35	35	50	55	55	75	20 Equal
M	56	10	5	10	5	15	10	35	35	60	60	10 Right
F	54	70	25	65	25	50	15	30	25	45	25	50 Right
M	58	20	20	20	20	20	0	35	45	50	60	15 Equal
M	60	0	0	0	0	10	10	25	15	50	50	10 Equal
F	53	5	10	10	5	15	15	30	45	35	45	10 Equal
F	55	30	25	15	10	20	15	35	15	40	20	NA
F	55	0	10	5	5	5	5	35	25	65	50	10 Left
M	57	25	5	40	25	35	15	45	45	55	60	35 Right
M	60	0	5	5	15	20	35	55	70	75	65	20 Left
M	57	10	5	10	5	5	5	35	45	45	70	10 Equal
M	57	15	35	15	35	20	70	75	95	75	85	35 Left
M	54	0	0	0	5	0	10	45	35	55	20	10 Left
F	48	0	0	0	0	10	0	15	10	15	25	5 Equal
M	52	5	5	10	0	0	0	15	15	60	50	10 Left
M	50	5	10	10	0	10	60	30	60	20	60	10 Equal
F	53	15	5	10	10	10	10	5	5	25	15	15 Right
M	52	20	25	25	30	25	40	30	35	20	25	35 Left

Abbreviations: F, female; M, male; NA, not available; SRT, speech reception threshold.

Table 2

Tinnitus Characteristics of the 18 Participants with Nonbothersome Tinnitus

	THI	Duration, y	Perceived Tone	Location	Loudness (0–10)
	4	6	Ringing; hum	Both	6
	12	8	Ringing; hissing	Both	4
	20	35	Ringing; high-tension wire	Right	5
	8	2	Hissing; buzzing	Both	3
	0	10	Ringing	Both	5
	8	10	Ringing; buzzing	Both	6
	8	5	Hum; high-tension wire	Right	3
	14	10	Ringing; high-tension wire	Both	4
	6	3	Ringing; whistle	Both	6
	4	15	Ringing	Both	5
	4	10	Clear tone	Left	2
	12	3	Ringing; cicadas	Both	4
	20	30	Ringing; hissing; transformer noise	Right	5
	4	1	Ringing	Both	7
	6	3	Ringing; clicking	Both	5
	14	12	Ringing	Left	5
	24	30	Ringing; crickets; high-tension wire	Both	7
	6	3.5	Clear tone	Left	2
Median	8	9			5

Abbreviation: THI, Tinnitus Handicap Inventory.