Tinnitus is associated with hyperactivity in the frontal lobe and reduced activity in the auditory cortex

Binu P Thomas[1,2], Kamakshi Gopal[3], Mira D'Souza[3], Deng Mao[1], and Hanzhang Lu[1]

[1]*Advanced Imaging Research Center, University of Texas Southwestern Medical Center, Dallas, Texas, United States,* [2]*Department of Bioengineering, University of Texas Southwestern Medical Center/University of Texas at Arlington, Arlington, Texas, United States,* [3]*Department of Speech and Hearing Sciences, University of North Texas, Denton, Texas, United States*

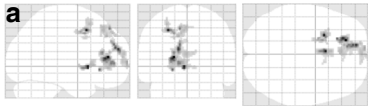
INTRODUCTION: Tinnitus is the perception of sound in the absence of an external stimulus. This sound can be a pure tone, narrow band noise or broadband noise. It is experienced by millions of people around the world; just in the US there are approximately 50 million people who suffer from this condition. Tinnitus is also the most widely reported disability among the veterans. Tinnitus is most often accompanied by hearing loss due to inner ear damage following exposure to loud sounds. Tinnitus can cause a lot of distress and disrupt day-to-day function. Yet the physiological mechanism is not well understood, and currently there is no cure for this condition. The current consensus among the researchers is that tinnitus originates in the brain. Hence, in this study we used MRI to compare brain function in patients suffering from tinnitus (tinnitus group), and age and gender-matched patients with comparable hearing but no tinnitus (control group). Three complementary MRI techniques were used: BOLD fMRI response to acoustic signals (pure tones matching the frequency of tinnitus and broadband noise), baseline cerebral blood flow (CBF) and resting state functional connectivity. We found that tinnitus patients showed hyper activations to both pure tones at the same frequency as that of their tinnitus, and broadband noise. The tinnitus group also showed lower resting CBF in the auditory cortex and posterior cingulate cortex compared to the control group. Thus, we believe that this condition may be attributed to hyper attention to sounds and reduced CBF in the auditory cortex and posterior cingulate cortex.

METHODS: EXPERIMENT: Tinnitus patients (N=6, age 52±10 years, range=38-65) and age, gender, and degree of hearing loss matched control volunteers (N=6, age 54±13 years, range=31-65) participated in this study. Each control volunteer was recruited as a matched pair for the tinnitus patient. All patients in the tinnitus group experienced tinnitus at a single frequency between 250 Hz to 8 KHz. All scans were performed on a 3T Philips system. Three MRI biomarkers were measured. *Functional brain activations* were measured using an auditory task that included frequency modulated pure tone stimulus at the frequency of tinnitus experienced by the patient and broadband noise. All participants performed the task in the scanner while (BOLD) MRI images were acquired using a "sparse-sampling" technique with following parameters: TR/TE = 10,000/30 ms, flip angle (FA) = 70°, field-of-view (FOV) = 220 × 220, matrix = 64 × 64, whole brain coverage with 39 slices, 4 mm thick, duration = 5 min. The sparse-sampling technique used a TR of 10,000 ms so as to deliver the auditory stimulus to the participant in the absence of scanner noise (1). The fMRI task was performed five times in the scanner to provide sufficient power to detect BOLD activations. *Resting CBF* was measured with a pseudo-continuous ASL (PCASL) sequence with following parameters: TR/TE=4250/14ms, label duration=1650ms, post label delay=1525ms, FOV = 240 × 240, matrix = 80 × 80, 29 slices, 5 mm thick, duration = 5 min 45s. *Resting state functional connectivity* in the brain was measured with a BOLD MRI sequence with following parameters: TR/TE = 2000/25 ms, FA = 80°, FOV = 220 × 220, matrix = 64 × 64, 43 slices, 3.5 mm thick, duration = 5 min. DATA ANALYSIS: Brain activations to the auditory task were detected for each subject using standard general linear model (GLM) analysis; and CBF map was generated using previously established procedures (2) (not detailed here due to space limitations). Differences between controls and tinnitus patients were detected using paired t-test comparisons and were deemed statistically significant at p=0.01 (unc.) and minimum cluster size of 100 voxels. Functional connectivity data were processed using established procedures; briefly, patient motion and white matter time course were regressed out and the data was band pass filtered between 0.01 to 0.1 Hz.

RESULTS AND DISCUSSION: Voxel-wise comparison of brain activations between control and patient groups revealed that tinnitus patients have hyperactivity in the frontal lobe (Fig.1) in superior frontal gyrus (BA 9), superior medial frontal and middle frontal gyrus and anterior cingulate in response to the pure tone stimulus at the same frequency of their tinnitus. This result may be interpreted as patient brains being hyper attentive to the pure tone sound at the frequency of tinnitus. The control volunteers did not show any regions in the brain with increased activity compared to the tinnitus patients. Brain activations to white noise with a broad frequency range revealed that tinnitus patients have hyperactivity in diffuse regions throughout the brain in inferior parietal lobule (BA 40), supramarginal gyrus (parietal lobe), parahippocampal gyrus, anterior cingulate, middle frontal gyrus and cerebellum. Again, the control volunteers did not show any regions with increased activity compared to the tinnitus patients in response to white noise. Thus this data reveals that tinnitus patients show hyper activations to any type of sound. Since we hypothesized that tinnitus patients have abnormal brain function in the auditory cortex, we performed region of interest (ROI) analysis using a mask of the auditory cortex. The auditory cortex mask was generated by obtaining a group activation map of all volunteers and obtaining only regions activated within the anatomically defined auditory cortex. We found that tinnitus patients showed 25% smaller BOLD signal change in the auditory cortex to pure tone compared to normal volunteers. We investigated if any CBF differences are present in the auditory cortex between groups and found that resting CBF in the auditory cortex was lower in the tinnitus patients by 15% compared to controls and the groups were significantly different at a p<0.05 (single-tail paired t-test), shown in Fig 2. To examine differences between left and right auditory cortices, we split the auditory cortex ROI into the left and right hemispheric sides and examined CBF in these ROIs. We found that CBF in tinnitus patients was lower in left and right auditory cortices by 11% and 18% respectively when compared to the control group. The CBF in the right auditory cortex was significantly different at p=0.002 (single-tail paired t-test) and this difference was confirmed in the voxel-wise comparisons of CBF maps between the tinnitus and control groups, shown in Fig. 3. We extracted the time course of resting state data from the left and right auditory cortex ROIs and obtained Pearson's correlation coefficient between the time courses and found no difference between groups.

CONCLUSIONS: The present work shows that tinnitus patients have hyperactivity in the frontal lobe to both pure tone and white noise, which was interpreted as patients being hyper attentive to sound. The tinnitus group also showed lower activations in the auditory cortex to both pure tone and white noise and this was interpreted as the auditory cortex being desensitized to sound due to the constant tinnitus that these patients experience. Resting CBF was also lower in the auditory cortex in the tinnitus patients which may be indicative of the abnormal brain function in the auditory cortex.

REFERENCES: 1) Gaab et al. Human Brain Mapping, 28: 703 (2007). 2) Chalela et al. Stroke, 31: 680 (2000)



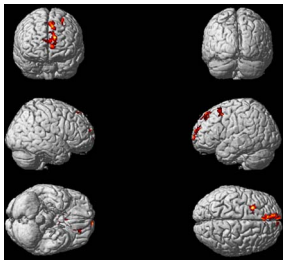


Fig. 1: Hyper activations in the Tinnitus (N=6) compared to control group (N=6), in response to the pure tone stimulus, significant at p = 0.01, minimum cluster size = 100 voxels. (a) Glass brain view shows that hyperactive regions are present only in the frontal lobe. (b) Activations rendered on a single subject brain for better visualization.

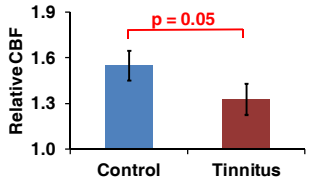


Fig 2: Relative CBF in the auditory cortex (relative to whole brain) in the Tinnitus (N=6) and control group (N=6)

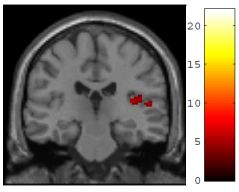


Fig. 3: Reduced CBF in the auditory cortex in the Tinnitus group (N=6) compared to control group (N=6), significant at p = 0.01, minimum cluster size = 100 voxels.