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14. ABSTRACT

Tinnitus is a major health problem among those currently and formerly in military service. This project hypothesizes that many of the clinically-significant, non-auditory aspects of the tinnitus condition involve two major brain networks: the cognitive control network (CCN) and the default mode network (DMN). Using fMRI, we are examining brain activation in subjects performing cognitive tasks that engage the CCN and DMN. One task is heavily reliant on working memory (N-back) and the other on selective attention (counting Stroop). Each task is conducted on auditory stimuli and, separately, on visual ones. A second version of the selective attention task includes emotional priming stimuli (fearful faces) so the effect of affect on CCN/DMN function can be assessed. Subjects in three groups are being compared: (1) control subjects with clinically-normal hearing thresholds and no tinnitus, (2) tinnitus subjects matched in hearing to the controls, (3) tinnitus subjects with bilateral high-frequency hearing loss. So far twenty-one subjects have been behaviorally tested and imaged. Preliminarily, the results support our hypothesis that people with tinnitus may exert greater cognitive effort in order to achieve the same level of outward performance as non-tinnitus controls on challenging cognitive tasks. The data are also beginning to suggest particular brain areas within the CCN, especially, that may warrant targeting for treatment and/or monitoring to quantify treatment efficacy.

15. SUBJECT TERMS
tinnitus, cognitive control network (CCN), default mode network (DMN), functional magnetic resonance imaging (fMRI)

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1. Introduction

The overall goal of this project is to test whether two major brain networks and their connections with auditory cortex play an important role in tinnitus. The networks are the cognitive control network (CCN) and default mode network (DMN). The specific aims are as follows:

Aim 1: During demanding cognitive tasks, test whether tinnitus subjects show greater engagement of the CCN and DMN than controls (i.e. physiological evidence of greater cognitive load).

fMRI activation will be measured during auditory and visual versions of two demanding tasks heavily reliant on working memory (N-back task) and selective attention (counting Stroop task). Control subjects will be compared to two groups of tinnitus subjects, both matched in age and sex to the controls and one matched in hearing threshold (clinically normal). A subset of subjects in each group will be matched in performance (accuracy and reaction time) so any dependence of activation on performance can be distinguished from that of tinnitus. Engagement of the CCN will be measured as increased image signal during task conditions relative to no task or reduced task load conditions ("positive" fMRI activation). Engagement of the DMN will be measured as the opposite i.e., reduced image signal during task conditions ("negative" activation).

Aim 2: Determine whether the reduced resting state functional connectivity between primary auditory cortex (PAC) and CCN/DMN in tinnitus subjects is reinstated
(a) during demanding tasks in the auditory domain, but not during tasks in the visual domain and,
(b) only when tinnitus is not perceived during the tasks.
For Aim 2a, fMRI data from Aim 1 will be used to assess PAC-CCN/DMN functional connectivity during task performance on auditory stimuli and, separately, on visual stimuli. For Aim 2b, following each scan, tinnitus subjects will report on their tinnitus during the tasks of that scan. These experiments will take an important step toward identifying ways to manipulate PAC – CCN/DMN connectivity and showing whether or not this connectivity is in fact crucial to the defining experience of tinnitus, the percept.

Aim 3: Test whether the influence of emotional priming on CCN and DMN function during a demanding cognitive task is greater in tinnitus subjects than controls.
During fMRI, subjects will perform the same selective attention task as in Aim 1 (counting Stroop, visual and auditory versions) but with the addition of a brief, visual priming stimulus before each trial. CCN and DMN engagement by the selective attention task, as well as functional connectivity within the CCN and DMN, will be compared between two types of primes, fearful and neutral faces, and further compared between controls and each of the two tinnitus groups.

Specific hypotheses tested by each aim:
(1) During attention-demanding tasks, there is an extra cognitive burden on tinnitus subjects that results in greater engagement of the CCN and DMN compared to non-

tinnitus controls.
(2) Functional connectivity between PAC and the CCN/DMN in tinnitus subjects will approach that of controls (a) during performance of demanding cognitive tasks performed in the auditory domain, but not during tasks in the visual domain and, (b) when tinnitus is not perceived during the tasks.
(3) The CCN and DMN are more susceptible to hijacking by the ventral affective network in tinnitus subjects than in non-tinnitus controls.

2. Keywords (and abbreviations)

- tinnitus
- cognitive control network (CCN)
- default mode network (DMN)
- primary auditory cortex (PAC)
- working memory
- selective attention
- emotional priming

3. Accomplishments

3.1 Activities in relation to Statement of Work

Activities in year 2 of this project have followed the SOW:

Development of experimental paradigm – No further progress necessary; completed in year 1.

Subject recruitment and testing – During the second year of this project, 31 subjects were recruited through ads in local and university newspapers, the MEEI website, and postings in local stores. Those meeting the study criteria went on to participate in three testing sessions:

Behavioral testing session in which audiograms are obtained, loudness growth and discomfort level are measured, tinnitus pitch, loudness are determined as well as the minimum level of broadband noise needed to mask the tinnitus percept (minimum masking level). Subjects are also familiarized with the tasks they will perform during fMRI.

fMRI session 1 in which subjects perform a working memory task ("2-Back") and a simple detection task ("Detect 1's") based on (a) visual and (b) auditory stimuli. Resting state fMRI data are also acquired unless the subject has become too uncomfortable or tired, in which case resting-state measurements are deferred to session 2.

fMRI session 2 in which subjects perform a selective attention task (Stroop) and a simple counting task based on (a) visual and (b) auditory stimuli. Subjects also perform the auditory version of the tasks in the presence of emotional priming (brief presentation of fearful faces). Resting-state data are obtained if they weren't already in session 1.

Subjects recruited fall into three groups, as originally proposed:

(1) NHcon - control subjects without tinnitus and with clinically-normal hearing thresholds ($\leq$ 25 dB HL from 250 – 4000 Hz, $\leq$ 35 dB HL at 8000 Hz).

(2) NHtin – tinnitus subjects matched in hearing threshold to the NHcon group.

(3) HFLtin – tinnitus subjects with bilateral high-frequency loss.

The distribution of participants across subject groups is summarized in Table 1. Mean audiograms for each group are given in Figure 1. All subjects are men, so the groups are automatically sex-matched. Subject ages range from 35 to 59. Mean ages for each group are 44 yrs (NHcon), 46 (NHtin), and 52 yrs (HFLtin).

Table 1: Summary of completed sessions in relation to project target.

	fMRI Sessions* Completed in Years 1,2	
	Session 1 N-Back	*Session 2 Stroop***
NH controls	18	17
NH tinnitus	16	14
HFL tinnitus	13	10
Total Completed	**47**	**41**
Project Target	**60**	**60**

* Resting state data are obtained during either session 1 or 2.

**Includes Stroop with emotional priming for Aim 3.

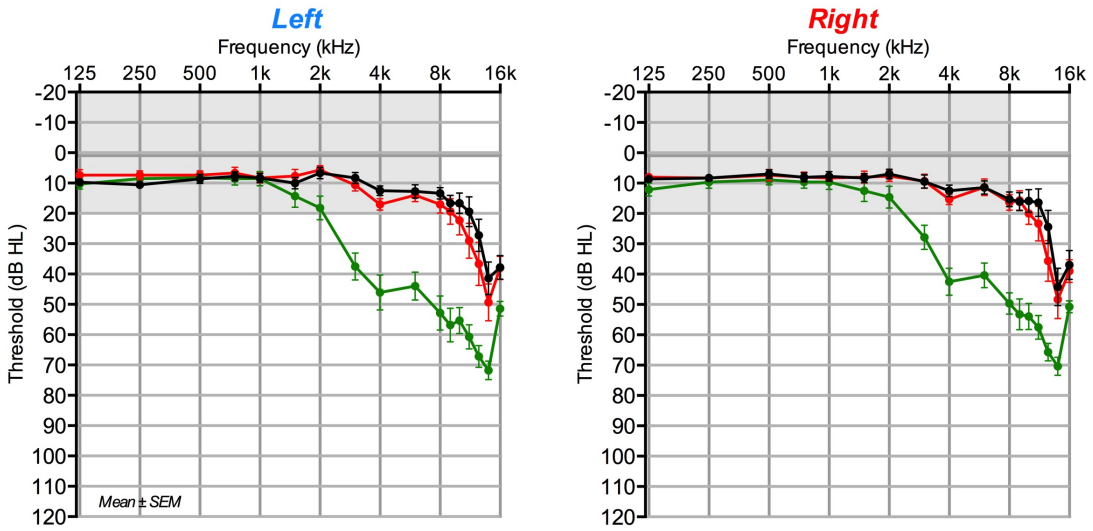

Figure 1: Mean of left and of right audiograms for subjects in each group: NH con (black), NH tin (red), HFL tin (green). Gray shading indicates clinically normal range. Error bars indicate +/- one SEM.

Data analysis – Using a combination of home-grown software and Statistical Parametric Mapping (SPM8; a freely available fMRI analysis package), fMRI and structural imaging data from each session were aligned to a standard brain atlas, corrected for subject motion and inspected for artifacts. Activation maps were created for various contrasts, including the most basic contrasts described in section 3.2 below.

3.2 Preliminary Results

Behavioral data - Subjects in all groups were able to perform the challenging tasks during both fMRI sessions. Occasionally, subjects performed unusually poorly on isolated fMRI runs, which are excluded from analyses below.

Analysis of the behavioral data taken during imaging showed little difference between subject groups in either response time or accuracy (calculated as 1 – (missed targets + false alarms)/total number of targets). This is important for the study design, which seeks to identify inter-group differences in brain activity that can't be attributed to differences in task performance. The similarity can be seen in the left panel of Figure 2 for the auditory version of the 2-back task of session 1. During the detect 1's task of session 1, subjects performed with perfect or near-perfect accuracy (i.e., accuracy = 1; not shown). The similarity in mean response time across subject groups can be seen in the right panel for both the detect 1's and 2-back tasks.

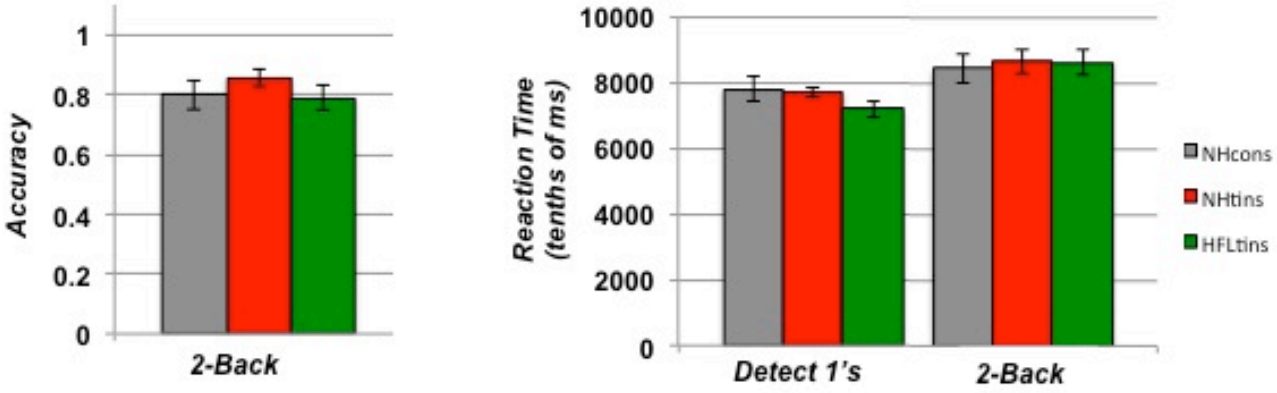

Figure 2: Accuracy and response time (RT) data from fMRI session 1 during which subjects detected 1's in some blocks and performed a 2-back task in others. Data are for auditory version of the tasks. Mean across subjects of each group: NHcon (gray bars), NHtin (red), HFLtin (green). Error bars indicate +/- one SEM.

fMRI data - Figure 3 shows maps of fMRI activation based on the session 1 data of NHcon, NHtin, and HFLtin subjects pooled. Specifically, image signal during the detect 1's and 2-back task conditions was contrasted with image signal during intervening periods of fixation (no task). The resulting contrast maps were then pooled across subjects to identify brain regions showing significant activity increases (i.e., image signal increases) during task conditions (colored regions in Figure 3). Sites showing activation comprise the cognitive control network, one of the two brain networks targeted in this project.

Regions showing a significant activity increase were then examined in second-level analyses to determine whether the activity increases differed between tinnitus subjects (NHtin and HFLtin) and controls (NHcon). When all subjects are considered together, there are no significant differences. However, there are still many analyses in

progress. For instance, analyses separating tinnitus subjects according to whether or not they heard their tinnitus during scanning, and according to level of tinnitus-related distress.

Analysis of data for the Stroop tasks and for resting state are also still in progress.

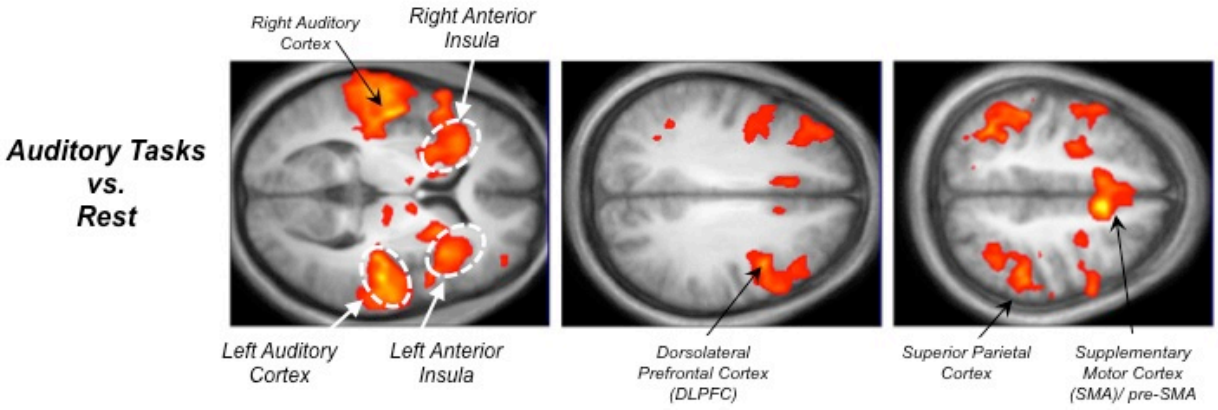

Figure 3: Cognitive control network. fMRI session 1 data. Axial brain slices showing activation maps based on auditory task conditions (detect 1's and 2-back) contrasted with no-task periods. Contrasts determined for individual subjects were pooled across subjects/groups in a second-level analysis. Color indicates brain areas of significant activity increase ($p <$ 0.0001, uncorrected) during task performance. Increasing significance is coded from red to yellow. The activation maps are superimposed on a mean of structural scans (average over subjects contributing to the activation maps).

3.3 Implication of results for the project hypotheses and future plans

The data obtained so far demonstrate that the project paradigms provide robust data for testing the study hypotheses.

The third and final year of this project will be spent acquiring the remaining data and then continuing to analyze and interpret the large amount of information obtained in our experiments.

4. Impact

This project is important for multiple reasons, including the fact that it stands to implicate particular brain networks and/or synergies between networks in the aspects of tinnitus that make tinnitus a clinical problem. Any well-controlled, quantitative physiological study of tinnitus has the potential for yielding a tinnitus biomarker. The proposed study is not an exception. Such a measure based on the present study paradigm holds special appeal because it could be used to objectively test the efficacy of therapies directed at improving the cognitive management of tinnitus, therapies based on attention tasks, or mind-body therapies such as meditation; in other words, therapies targeting networks that transform the tinnitus percept from benign to problematic.

5. Changes/ Problems

There have been no major changes to this project. The following minor change was made in year 2 to improve subject recruitment: Subjects were offered a 3D printed model of their brain as additional compensation. This was approved by the Mass Eye and Ear IRB before it was implemented.

Also, the following minor changes initiated in year 1 were continued in year 2:

(1) Because subjects' time in the scanner was proving too long: (a) resting state fMRI data is being obtained during one instead of both of the fMRI sessions, and (b) effects of emotional priming (Aim 3) on auditory (but not visual) task performance is being examined.

(2) Subjects have been recruited via flyers posted widely throughout Boston and surrounding communities instead of via subway ads (as originally proposed) in order to diversify the demographics of people inquiring about participation. Funds originally planned for subway recruitment ads were used to provide the 3D printed brains instead which have proven to be of more interest than monetary compensation to many subjects. Note that subjects still receive the same monetary compensation; the 3D brain is in addition.

6. Products

None.

7. Participants & Other Collaborating Organizations

The human subject testing for this project has been approved by HRPO.

8. Special Reporting Requirements

None.

9. Appendices

None.