AWARD NUMBER: W81XWH-13-1-0491

TITLE: Default, Cognitive, and Affective Brain Networks in Human Tinnitus

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REPORT DATE: December 2016

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE
December 2016

2. REPORT TYPE
Final

3. DATES COVERED
30 Sep 2013 - 29 Sep 2016

4. TITLE AND SUBTITLE

Default, Cognitive and Affective Brain Networks in Human Tinnitus

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-13-1-0491

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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Boston, MA 02114

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

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)

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
					USAMRMC
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
Unclassified	Unclassified	Unclassified	Unclassified	11	

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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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; Binder et al., ’99; Raichle et al., ’01; Fox et al., ‘05). 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; Conway et al., ‘05) and selective attention (counting Stroop task; Bush et al., ’98). 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)
- right anterior insula (a node in the CCN)
- primary auditory cortex (PAC)
- working memory
- selective attention
- emotional priming

3. Accomplishments

3.1 Activities in relation to Statement of Work

Activities during this project followed the SOW:

Development of experimental paradigm

Completed in year 1.

Subject recruitment and testing

Participants were recruited through ads in local and university newspapers, the MEE website, and postings in local stores.

Participants fell into three groups, as originally proposed:

(1) NH-con - 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) NH-tin – tinnitus subjects matched in hearing threshold to the NHcon group.

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

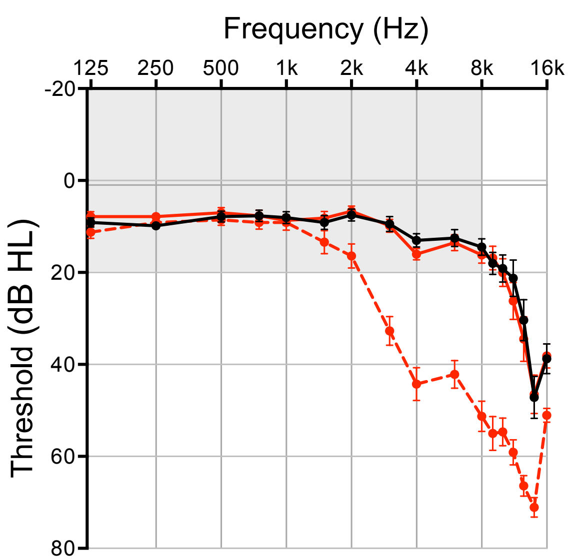

Figure 1: Mean audiogram for subjects (all men) in each group: NH con (black; 18 subj.), NH tin (red, solid; 16), HFL tin (red, dashed; 13). Gray shading indicates clinically normal range. All subjects were men ranging in age from 35 to 59. Audiogram for the right and left ear were first averaged for each subject; audiograms were then averaged across subjects. Audio Error bars indicate +/- one SEM.

The testing sessions for each participant were as follows:

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).

fMRI session 1 in which participant performed a working memory task (“2-Back”) and a simple detection task (“Detect 1’s”) based on (a) visual and (b) auditory stimuli (Figure 2). Resting state fMRI data were also acquired unless the participant was too uncomfortable or tired, in which case resting-state measurements were deferred to session 2, or performed in a third session, if necessary.

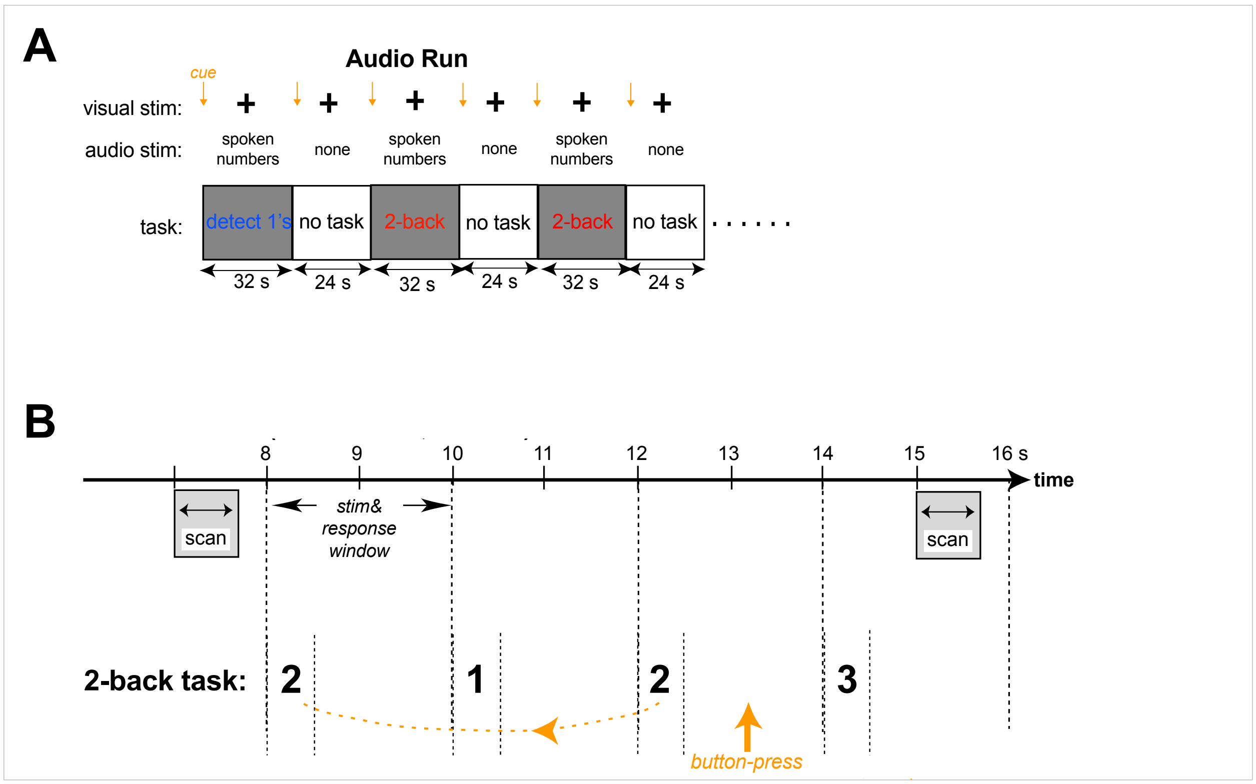

Figure 2: Paradigm for N-back task performed in fMRI session 1. (A) Summary of a auditory N-Back run. Auditory stimuli (spoken numbers) were presented over headphones during task blocks (2-back or detect 1’s), which were separated by blocks in which no task was performed. At the beginning of each block, a visual cue was briefly displayed indicating the task (if any) to be performed in the subsequent block (e.g., “detect 1’s”). Visual N-back runs were the same except there was no auditory stimulus and numbers were displayed instead of spoken.
(B) Detailed timing of scans, stimulus presentation and behavioral response. Participants were instructed to respond by pressing a button whenever they heard (audio task) or saw (visual task) a number was the same as the number “2 back”.

fMRI session 2 in which participants performed a selective attention task (Stroop) and a simple counting task based on (a) visual and (b) auditory stimuli. Participants also performed the auditory version of the tasks in the presence of emotional priming (brief presentation of fearful faces). Resting-state data were obtained if they weren't already in session 1. Note that the fMRI Stroop data from this session showed no differences across participant groups, so the remainder of this report will focus on the N-back fMRI data from session 1.

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 Results and Discussion

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 was important for the study design, which sought to identify inter-group differences in brain activity that can't be attributed to differences in task performance. The similarity across groups can be seen in Figure 3 for the 2-back task of fMRI session 1. During the detect 1's task of this session, participants performed with perfect or near-perfect accuracy (i.e., accuracy = 1; not shown) whereas during the 2-Back task accuracy was 0.75 – 0.8, indicating that the task was doable, but required effort.

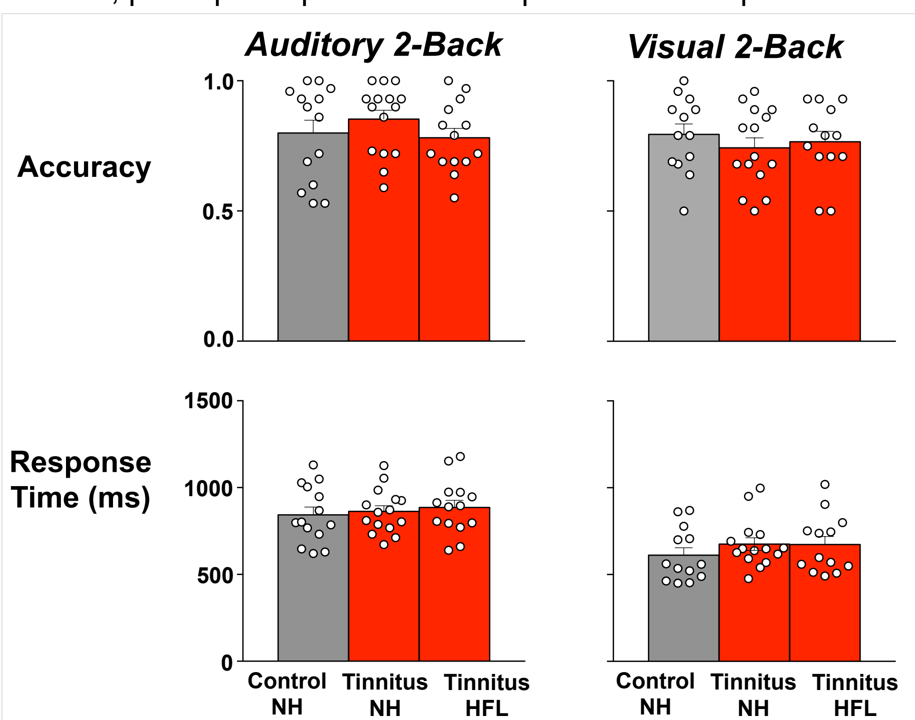

Figure 3: No significant inter-group differences in mean accuracy or response time (RT) during the 2-back task of fMRI session 1. Open circles correspond to individual subjects. Error bars indicate +/- one SEM.

fMRI data

Figure 4 shows maps of fMRI activation based on the session 1 data of NH-con, NH-tin, and HFL-tin participants 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 participants to identify brain regions showing significant activity increases (i.e., image signal increases) during task conditions (colored regions in Figure 4). Sites showing activation comprise the cognitive control network, one of the two brain networks targeted in this project. The other targeted network, the DMN, was revealed in an opposing contrast showing sites of significant activity decreases (not shown).

The contrast maps just described (task conditions vs. no task) were then subjected to second-level analyses testing for differences across groups. Significant differences were not found. Thus, neither the CCN nor the DMN showed differences between participant groups in whole brain analyses.

While statistically significant differences were not seen between groups in the whole brain analyses, one brain region, right anterior insula, showed a trend toward greater activity in the tinnitus groups NH-tin, HFL-tin. A region of interest analysis was therefore conducted to examine whether the greater activity occurred in a definable subset of tinnitus participants such as those with high (or low) depression, anxiety, tinnitus-related distress and whether or not tinnitus was heard while performing the tasks (based on participant report immediately following scanning). The latter factor, whether or not tinnitus was heard, proved to be related to right insular activity increases. This can be seen in Figure 5 showing the result of a whole brain contrast between the subset of tinnitus participants (NH-tin and HFL-tin) who reported hearing their tinnitus while performing the task and controls (NH-con).

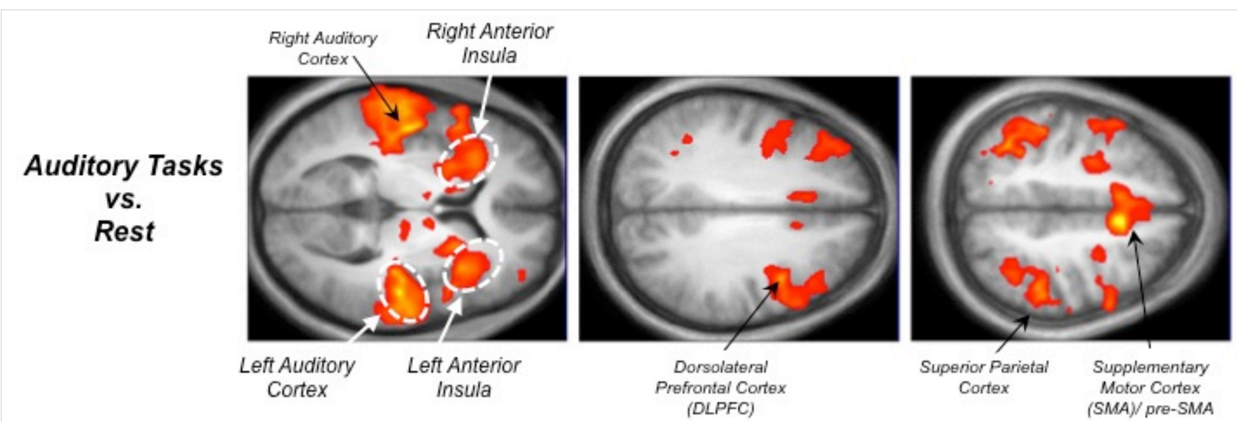

Figure 4: Cognitive control network revealed by N-back data from fMRI session 1. Axial brain slices showing activation maps based on auditory task conditions (detect 1's and 2-back) contrasted with no-task periods. Contrasts determined for individual subjects were pooled across subjects/groups in a second-level 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).

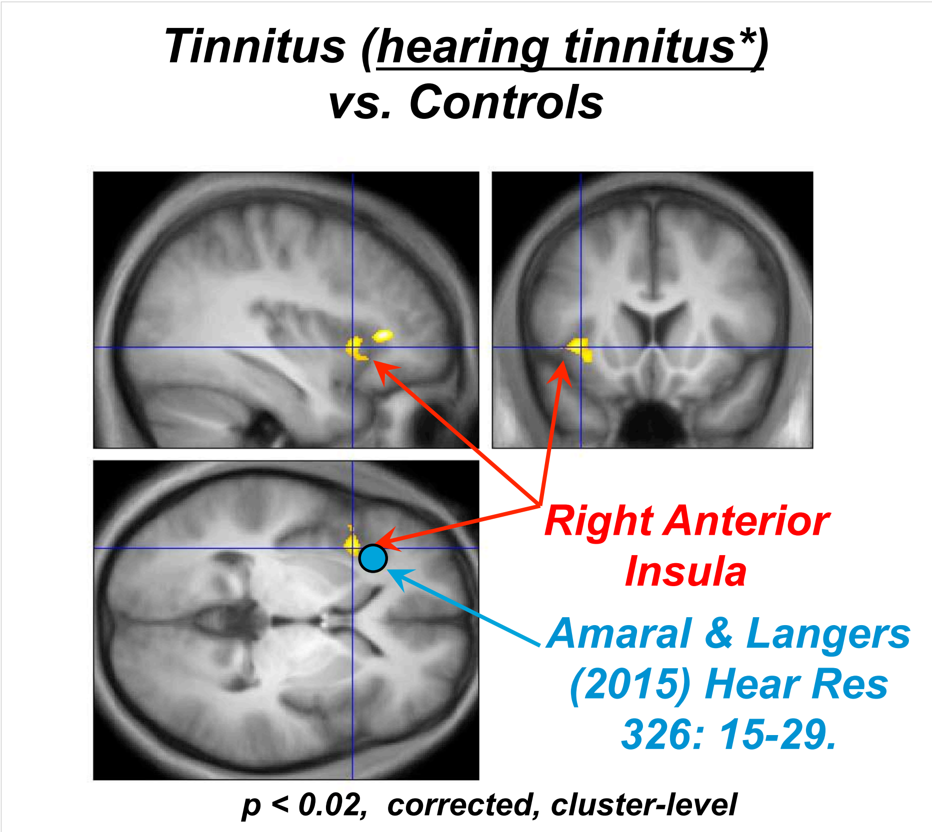

Figure 5: Greater right anterior insula activation in tinnitus participants who heard their tinnitus during task performance compared to controls. Sagittal, coronal, and axial slices through anterior insula are shown superimposed on an across-subject average of anatomical scans (grayscale). Also indicated is a region found previously to show differences between tinnitus and non-tinnitus groups on a similar cognitive task (Amaral and Langers, 2015). This previous finding supports the present study in implicating right anterior insula in tinnitus, but unlike the present study did not go further to identify a link to conscious perception of tinnitus.

The present results implicate right anterior insula, a brain area part of the CCN in tinnitus. A previous study also provides evidence for anterior insular involvement in tinnitus (see site identified by Amaral and Langers, 2015 in Figure 5). However, the present study is, to our knowledge, the first to link conscious perception of tinnitus to activity levels in the right anterior insula.

There are various possible explanations for this result. One is that insular activity and tinnitus perception are not causally linked but instead result from aberrant activity in an as-yet unidentified brain area. Another possibility is that hearing tinnitus during task performance increased task difficulty (although not to the point of diminishing behavioural measures of performance, see Figure 2). In this case, greater task-related insular activity in people who reported hearing their tinnitus might reflect greater effort needed to focus attention on the tasks instead of the tinnitus percept.

3.4 References

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3.5 Dissemination of Findings

The PI presented the findings above as parted of her invited Lecture on Tinnitus at AudiologyNOW! in 2016 (Phoenix, AZ).

4. Impact

This project is important in linking activity in a particular brain area, right anterior insula, to conscious perception of tinnitus. Any well-controlled, quantitative physiological study of tinnitus has the potential for yielding a tinnitus biomarker. The proposed study is not an exception. Activity levels within a node of the CCN (right anterior insula) 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 intended to the tendency of tinnitus sufferers to "latch onto" and listen to the tinnitus percept.

5. Changes/ Problems

The following changes were made over the course of the project:

(1) Participants' time in the scanner proved to be too long. This was intially addressed by only acquiring resting state fMRI data in one of the two fMRI sessions instead of both. But session duration continued to be a problem, such that the emotional priming run during session 2 often could not be pterformed because of subject discomfort. With that still not being enough to solve the session duration/ participant

discomfort problem, a third fMRI session was added for performance of resting state runs. Note that the additional cost of these extra sessions meant it was necessary to scan fewer participants than originally planned.

(2) Participants were 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. Note that participants still received 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 was approved by HRPO.

8. Special Reporting Requirements

None.

9. Appendices

None.