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TITLE: Identifying Subgroups of Tinnitus Using Novel Resting State fMRI Biomarkers and Cluster Analysis

PRINCIPAL INVESTIGATOR: Fatima Husain, PhD

CONTRACTING ORGANIZATION: University of Illinois
                              Urbana, IL 61801

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6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

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

University of Illinois
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The subject of the project is FY14 PRMRP Topic Area – Tinnitus. The broad goal of this project is to link behavioral measures of tinnitus severity to brain imaging scans that target areas of auditory, attention, and emotion processing, which are important to the underlying neural mechanisms of tinnitus. This study uses functional magnetic resonance imaging (fMRI) and is taking place at the University of Illinois at Urbana-Champaign (UIUC) for civilian data collection (patient and control) and at Wilford Hall Ambulatory Surgical Center (WHASC) for military data collection (patient and control). Identical audiological, behavioral, and brain imaging protocols are being used at both sites and include patients with a range of tinnitus severity. In Year 1, we have begun to use resting-state fMRI to identify measurable characteristics of functional connectivity in attention, emotion, and auditory processing networks that are exclusive to the tinnitus population. In Year 2, we will use clustering algorithms applied to the resting-state data to identify tinnitus subgroups within the patient population and pair them with specific behavioral characteristics.

15. SUBJECT TERMS
fMRI (functional magnetic resonance imaging), tinnitus, brain imaging, cluster analysis, active duty service members, resting-state fMRI, UIUC, WHASC

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**	Unclassified	14	**19b. TELEPHONE NUMBER** *(include area code)*
Unclassified	Unclassified	Unclassified			

Table of Contents

1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

The subject of the project is FY14 PRMRP Topic Area – Tinnitus. The broad goal of this project is to link behavioral measures of tinnitus severity to brain imaging scans that target areas of auditory, attention, and emotion processing, which are important to the underlying neural mechanisms of tinnitus. We will also apply advanced mathematical clustering techniques to further elucidate these mechanisms. This study will use functional magnetic resonance imaging (fMRI) and will take place at the University of Illinois at Urbana-Champaign (UIUC) for civilian data collection (patient and control) and at Wilford Hall Ambulatory Surgical Center (WHASC) for military data collection (patient and control). Identical audiological, behavioral, and brain imaging protocols will be used at both sites and will include patients with a range of tinnitus severity. We intend to use resting-state fMRI to identify measurable characteristics of functional connectivity in attention, emotion, and auditory processing networks that are exclusive to the tinnitus population. We will also use clustering algorithms applied to the resting-state data to identify tinnitus subgroups within the patient population and pair them with specific behavioral characteristics. To effectively identify objective biomarkers of tinnitus severity, the participants will complete fMRI scans twice, exactly one week apart, to investigate the reliability of the resting-state fMRI. At the end of the study, we expect to know the common and invariant neural correlates of tinnitus across subgroups in both military and civilian patient populations and also the relevant differences. The immediate outcome of the study is furthering our knowledge of neural correlates of tinnitus and of resting-state fMRI as an objective tool to diagnose and characterize tinnitus. The study will further serve as a baseline for testing interventions, such as modulation of tinnitus by sounds, electrical or magnetic stimulation, psychological therapies or pharmacological drugs.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

fMRI (functional magnetic resonance imaging), tinnitus, brain imaging, cluster analysis, active duty service members, resting-state fMRI, UIUC, WHASC

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.*

   o **What were the major goals of the project?**

      ▪ *List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project identify these dates and show actual completion dates or the percentage of completion.*

- **Specific Aim 1: Identify functional biomarkers of tinnitus severity using resting state functional connectivity.**
   o Proposed timeline of progress of Aim 1:
      ▪ 1-6 months:
         - Task 1: Prepare regulatory documents and research protocol for Aim 1
            o Refine eligibility criteria, exclusion criteria, screening protocol (same for both sites)
            o Finalize consent form & human subjects protocol at both UIUC and WHASC

- o Actual completion date: UIUC (9/21/2015), WHASC (9/9/2016). Details in next section.

  - ▪ 6-9 months:
    - • Task 2: Participant recruitment, participant evaluation, MRI and behavioral data acquisition
      - o Begin data collection
      - o Number of total completed subjects expected:
        - ▪ UIUC: N = 20 patients and 10 controls
        - ▪ WHASC: N = 10 patients and 5 controls
      - o For details on actual number of subjects on whom data has been collected, see next section.
      - o *Milestones to achieve:*
        - ▪ Study 1 begins
        - ▪ 1st participant consented, screened and enrolled, and data compared across both sites.
        - ▪ Actual completion date: UIUC (1/8/2016), WHASC (9/14/2016)

  - ▪ 9-27 months:
    - • Task 3: Ongoing data collection.
      - o Number of total completed subjects expected:
        - ▪ UIUC: N = 60 patients and 30 controls
        - ▪ WHASC: N = 40 patients and 20 controls
      - o For year 1 (at end of first 12 months) details see next section.
    - • Task 4: Behavioral and MRI data analysis:
      - o Transfer HCE/WHASC data regularly to UIUC
      - o Ongoing data processing and analysis to monitor data quality
      - o For year 1 (at end of first 12 months) details see next section.

  - ▪ 24-36 months:
    - • Task 5: Dissemination of results:
      - o *Milestone to achieve*:
        - ▪ Co-author manuscripts on fMRI and behavioral data

- **Specific Aim 2: Determine tinnitus subgroups using automated cluster analysis of resting state data and associate the subgroups with behavioral characteristics and neural mechanisms.**

- o Proposed timeline of progress of Aim 2:
  - ▪ 9-18 months:
    - • Task 1: Refine the topological data analysis and clustering method previously developed to apply to current tinnitus data set
      - o Percentage of completion at end of Year 1 (12 months): 50%
  - ▪ 18-36 months:
    - • Task 2: Separate the tinnitus patient group and the control group into two groups
      - o *Milestone to achieve:*
        - ▪ Co-author paper on dissociating tinnitus from control groups based on blind, automated methods
    - • Task 3: Cluster the larger tinnitus population into separate sub-groups based on imaging data; test for differences between civilian and military population
      - o *Milestone to achieve:*
        - ▪ Co-author paper on the various subgroups of tinnitus based on brain imaging measures

What was accomplished under these goals?

- ▪ *For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.*

Accomplishments under these goals:
- • **Specific Aim 1: Identify functional biomarkers of tinnitus severity using resting state functional connectivity.**
  - o Actual timeline of progress of Aim 1:
    - ▪ Task 1: Prepare regulatory documents and research protocol for Aim 1
      - • Eligibility criteria, exclusion criteria, and behavioral protocol was finalized for use at both sites

        - o Kick-off meeting held at WHASC in January 11-14, 2016, with PI and Co-PIs being present (Drs. Husain, Esquivel, Sherman and additional staff: Elsa Camou, Sara Schmidt, Erin Sheffer, Pedro Ramos, Kelly McKay); data acquisition protocols and inclusion/exclusion criteria were discussed.
          - ▪ Audiological research protocols were installed and tested on WHASC equipment.
        - o Consultation with Dr. Tyler (from University of Iowa) via an in-person visit to modify research protocol was completed on November 11th, 2015.
        - o A second visit from Dr. Tyler occurred on May 5th-6th, 2016 to confirm the protocol and preliminary behavioral data collection
      - • IRB and HRPO approval was achieved at UIUC.
        - o IRB approval: 8/3/2015
        - o HRPO approval: 9/21/2015

- o UIUC IRB protocol was amended to include minor alterations to protocol, including updated questionnaires; approval granted on 12/14/2015. Amendment was minor and did not require HRPO approval.
- o UIUC IRB protocol was successfully renewed on Jul 26, 2016 and information sent to HRPO.

- IRB approval at WHASC
  - o The CRADA between The Geneva Foundation and WHASC was submitted and is legally sufficient with an execution date of January 2016 and fully executed as of 7 March 2016. The agreement was recorded under DTTIS #: 16-066-HCE-C15038, and from now on, this agreement will be officially tracked and archived by this number.
  - o HCE/WHASC protocol and HRPO application were submitted in March 2016 to the USAMRMC IRB and final approval obtained September 9, 2016.
- Data transfer method from WHASC to UIUC was proposed and tested with pilot MRI data both in January 2016 and September 2016.
- Research audiologist, Charla Levy, AuD, was hired at WHASC to assist with patient recruitment and data collection on 7/11/2016.
- A second visit to WHASC with PI and Co-PIs being present (Drs. Husain, Esquivel, Sherman and additional staff: Elsa Camou, Sara Schmidt, Charla Levy, Pedro Ramos, Kelly McKay) occurred 6-8, September 2016
  - o MRI and behavioral protocols were finalized.
  - o Pilot data for 2 participants were collected during the visit. Data was compared with UIUC's and found to be satisfactory. Upon conclusion of visit, data collection was ready to begin.

- Task 2: Participant recruitment, participant evaluation, MRI and behavioral data acquisition

  - At UICU, an e-week (internal UIUC newsletter) announcement for recruiting controls was sent on April 24th, 2016; another one for recruiting patients was sent on June 12th, 2016.
  - Behavioral data collection began at UIUC on schedule.

    - o First participant was consented, screened and enrolled on January 8th, 2016.

    - o By September 14th, 2016, behavioral data were collected on 50 human subjects, including 31 patients and 19 controls. 18 additional subjects have been contacted for initial screening. Recruitment and data collection are ongoing.

  - MRI data collection at UIUC was delayed due to an upgrade of the scanner at UIUC.

    - o First subjects' data (6 individuals, 3 patient and 3 control) were collected in March-May 2016

    - o Data collection began on the upgraded magnet in early July, 2016

- By September 14th, 2016, MRI data (both visits) were collected on 15 participants (11 patients, 4 controls). 10 additional subjects were in the process of being scheduled for MRI data collection.

- Data collection at WHASC was delayed due to a delay in receiving IRB approval.

    - Pilot data was collected during both site visits to WHASC; MRI data was collected a total of three individuals.

    - As of September 2016, 1 patient and 3 controls have been consented and enrolled to participate. With data collection scheduled September – November 2016.

    - Recruitment and data collection are ongoing.

- Task 3: Behavioral and MRI data analysis

    - Preliminary data analysis of the 11 tinnitus participant MRI data collected at UIUC suggests that the resting-state functional connectivity does replicate. No differences in the connectivity between the two participant visits were observed. This will allow us to now employ cluster analysis in the next year

    - Preliminary data analysis of the behavioral results on 10 normal hearing tinnitus participants collected at UIUC suggests that the performance of behavioral testing was not affected by tinnitus severity measured with the Tinnitus Handicap Inventory questionnaire.

    - Descriptive analysis of the tinnitus group revealed a mean pure tone average (PTA; average of pure tone frequencies 0.5, 1, 2, and 4 kHz) to be 24 dB HL for both ears (std. dev. =13 dB) with 15 dB HL as the lowest PTA and 66 dB HL as the highest. Control participants will be recruited to match the hearing loss profiles of the tinnitus group. Additionally, scores on the Tinnitus Handicap Inventory (THI) for the tinnitus group ranged from 0 to 84 with a mean score of 23 (std. dev. =18).

- **Specific Aim 2: Determine tinnitus subgroups using automated cluster analysis of resting state data and associate the subgroups with behavioral characteristics and neural mechanisms.**
    - 9-18 months:
        - Task 1: Refine the topological data analysis and clustering method previously developed to apply to current tinnitus data set.
            - Monthly in-person meetings between collaborators Husain, Baryshnikov, Hirani and graduate students working on Aim 2 have been initiated, as of June 2016.
            - Refinement of analytical methods has begun and is about 50% complete.

What opportunities for training and professional development has the project provided?

- The WHASC Radiology research team received on-site Esys training. The training provided information how to install custom paradigms that would benefit the research project in future (if required). Furthermore, the team was provided educational materials to facilitate programming paradigms on the system.
- Pedro Ramos visited UIUC March 20th, 2016 to receive training re. data collection from the MRI technologists and researchers at the Biomedical Imaging Center at UIUC.

How were the results disseminated to communities of interest?

The following activities were undertaken o disseminate preliminary research data to communities of interest and to obtain feedback. One poster was presented at the Society for Neurosicence conference in 2016.

Schmidt, S. A., Schubel, M., Hirani, A. N., Baryshnikov, Husain, F.T. Unsupervised hierarchical clustering of resting state functional connectivity data to identify patients with mild tinnitus. Poster session presented at: Society for Neuroscience, 2015; 2015 October 17-21; Chicago, IL.

Two talks were given at the Tinnitus Research Initiative Conference, 2016:

Husain, F.T., Romero, A., Schmidt, S.A. Investigating tinnitus subgroups varying in severity using Diffusion Tensor Imaging Paper presented at: Tinnitus: subtypes, mechanisms and interventions. 10th TRI Tinnitus Conference; 2016 March 16-18; Nottingham, UK.

Schmidt, S.A., Carpenter-Thompson, J.R., Husain, F.T. Decreased default mode network connectivity to the precuneus is common across tinnitus subgroups. Paper presented at:

Tinnitus: subtypes, mechanisms and interventions. 10th TRI Tinnitus Conference; 2016 March 16-18; Nottingham, UK.

What do you plan to do during the next reporting period to accomplish the goals?

If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

The main goal for Year 2 is to continue with data collection at both sites. Now that both sites' protocols are approved and UIUC has collected their first set of data, we can focus on data collection. At WHASC, we have obtained permission for 3 hrs/week dedicated time on the scanner (2 scans/week). Similarly at UIUC, we have dedicated time of 4.5 hrs/week (3 scans/week). We have staff at both sites to perform data collection and analysis. We have overcome the initial setbacks relating to IRB approval and delays due to magnet upgrades. We do not foresee other impediments to data collection in the short-term. Methods have been employed at both sites to gather a range of tinnitus severity among participants.

Analyses of both MRI and behavioral data has begun and in continuing. Two abstracts of preliminary data for both behavioral and fMRI portions were submitted to the Association for Research in Otolaryngology (ARO) on September 15th, 2016. Poster/podium presentations are expected during Association for Research in Otolaryngology's 39th midwinter meeting on February 20th-24th, 2017.

We have begun the work on checking replicability of data at UIUC and will now begin similar work at WHASC and compare results across centers. We intend to submit a paper on replicability results in the coming year.

We have begun preliminary work on Aim #2 with current data collection and we will begin work on clustering analysis. Once this analysis has progressed sufficiently, we will present our initial results at conferences in the coming year and obtain feedback from the scientific community.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

    o **What was the impact on the development of the principal discipline(s) of the project?**

        ▪ *Nothing to Report*

    o **What was the impact on other disciplines?**

        ▪ *Nothing to Report*

    o **What was the impact on technology transfer?**

        ▪ *Nothing to Report*

    o **What was the impact on society beyond science and technology?**

- ▪ *Nothing to Report*

5. **CHANGES/PROBLEMS:** *The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

   o **Changes in approach and reasons for change**

      - ▪ *Nothing to Report*

   o **Actual or anticipated problems or delays and actions or plans to resolve them**

      - ▪ *Describe problems or delays encountered during the reporting period and actions or plans to resolve them.*

      - ▪ We encountered unanticipated delays at both data collection sites.

         - ▪ At UIUC, an upgrade to the MRI scanner took 5 months to be completed, which delayed data collection considerably. However, scanner is now up and running and MRI data on 15 participants has been collected. We do not expect any further interruptions to the data collection timeline.

         - ▪ At WHASC, the IRB approval and the HRPO approval process was lengthier than predicted and restricted data collection, resulting in a delay. Approvals are complete and data collection has begun.

   o **Changes that had a significant impact on expenditures**

      - ▪ *Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.*

      Nothing to report

   o **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

      - ▪ *Nothing to Report*

6. **PRODUCTS: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."**

   o **Publications, conference papers, and presentations**
   Report only the major publication(s) resulting from the work under this award.

      - ▪ **Journal publications.** *Nothing to Report*

      - ▪ **Books or other non-periodical, one-time publications.** *Nothing to Report*

- **Other publications, conference papers, and presentations.** *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

   Nothing additional to report—see "dissemination of results" earlier in report

- **Website(s) or other Internet site(s)**
  Nothing to Report

  Technologies or techniques
  Nothing to Report

  Inventions, patent applications, and/or licenses

  Nothing to Report

  Other Products
  Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

  - *Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."*

Name: *Fatima Husain, Ph.D.*
Project Role: *Primary director*
Research Identifier: *orcid.org/0000-0001-5878-3851*
Nearest person month worked: *0.5*
Contribution to Project: *Dr. Husain worked on all aspects of the project including drafting of IRB behavioral and scanning protocols, advising on recruiting and initial data collection. She also supervised analysis of data and the submission and presentation of conference poster on pilot data for the project.*

Name: *Sara Schmidt*
Project Role: *Graduate Student*
Research Identifier: *orcid.org/0000-0002-0161-8350*
Nearest person month worked: *1.5*
Contribution to Project: *Ms. Schmidt worked on establishing the scanning protocols and questionnaires to be used during behavioral testing and scanning*

for both sites. She also worked on drafting the IRB documents, assisted with recruitment procedures, and presented the conference poster and one of the talks at TRI 2016. She is overseeing the MRI data collection at UIUC and performed the preliminary analysis examining replicability.

Name: *Yihsin Tai, AuD*
Project Role: *Graduate Student*
Research Identifier: *orcid.org/0000-0002-7239-1915*
Nearest person month worked*: 1.5*
Contribution to Project: *Ms. Tai has performed work in purchasing new equipment, developing on-site healthcare form and protocol for behavioral testing and data acquisition, evaluating tinnitus related questionnaires for the current project, and coordinating recruitments for potential participants. She also conducted the behavioral testing and preliminary analysis of the behavioral data.*

Name: *Anthony Tsao*
Project Role: *Graduate Student*
Research Identifier: *orcid.org/0000-0003-2426-4476*
Nearest person month worked*: 0.75*
Contribution to Project: *Mr. Tsao helped establish protocol for behavior testing, coordinate with WHASC, and update the Auditory Cognitive Neuroscience Lab website with more current information. He also conducted behavioral testing.*

Name: *Carlos Esquivel, M.D.*
Project Role: *HCE/WHASC Principal Investigator*
Research Identifier: *In process*
Nearest person month worked: *0.15*
Contribution to Project: *Dr. Esquivel helped draft the required CRADA and research protocol at WHASC. He will supervise recruitment and collection of behavioral data at WHASC.*

Name: *Paul Sherman, M.D.*
Project Role: *HCE/ WHASC Associate Investigator*
Research Identifier: *orcid.org/0000-0002-9910-6889*
Nearest person month worked*: 0.15*
Contribution to Project: *Dr. Sherman helped draft the required CRADA and research protocol at WHASC. He will facilitate collection of MRI data.*

Name: *Pedro Ramos*
Project Role*: HCE/ WHASC MRI Technologist*
Research Identifier*: In process*
Nearest person month worked*: 0.15*
Contribution to Project: *Mr. Ramos assisted with the imaging and research protocol at WHASC and visited UIUC on March 30, 2016, to ensure across site consistency in data collection. He (with TSgt Kelly McKay) will be responsible for running the MRI scans at WHASC.*

Name: *Elsa Camou, MPH*
Project Role: *HCE/WHASC Research Coordinator*

Research Identifier: *orcid.org/0000-0001-6627-6884*
Nearest person month worked: *0.6*
Contribution to Project: *Ms. Camou worked with the Geneva Foundation and the AFMS ORTA on the creation and execution of the CRADA. Furthermore, she assisted with the creation of the HCE/WHASC research protocol and HRPO application.*

Name: *TSgt Kelly McKay*
Project Role: *HCE/ WHASC MRI Technologist*
Research Identifier*: In process*
Nearest person month worked*: 0.15*
Contribution to Project: *TSgt McKay assisted with the imaging and research protocol at WHASC. She (with Pedro Ramos) will be responsible for running the MRI scans at WHASC.*

Name: *Charla Levy, AuD*
Project Role: *HCE/WHASC Research Audiologist*
Research Identifier: *orcid.org/ 0000-0003-1423-3713*
Nearest person month worked*: 0.6*
Contribution to Project: *Dr. Charla Levy assisted with behavioral and audiological testing, creation of research tools, and participant recruitment, as well as data entry. Dr. Levy will be in charge of behavioral data collection at WHASC and will also assist with MRI data collection.*

Name: *Erin Sheffer, AuD*
Project Role: *HCE/WHASC Research Audiologist*
Research Identifier: *orcid.org/0000-0001-6627-6884*
Nearest person month worked*: 0.75*
Contribution to Project: *Dr. Sheffer assisted with the creation of the HCE/WHASC research and audiological protocol until August 2016, at which time she left HCE/WHASC. She will have no further involvement with the project.*

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

  - *Nothing to Report*

- **What other organizations were involved as partners?**

  - *Nothing to Report*

8. **SPECIAL REPORTING REQUIREMENTS**

    o **COLLABORATIVE AWARDS:** *For collaborative awards, independent reports are required from* **BOTH** *the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to https://ers.amedd.army.mil for each unique award.*

        ▪ **Not applicable.**

    o **QUAD CHARTS:** *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

        ▪ **See attached.**

9. **APPENDICES:** *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc. Reminder: Pages shall be consecutively numbered throughout the report.* **DO NOT RENUMBER PAGES IN THE APPENDICES.**

        ▪ *Nothing to Report*

Identifying Subgroups of Tinnitus Using Novel Resting fMRI Biomarkers and Cluster Analysis

PI: Husain, Fatima   **Org:** University of Illinois at Urbana-Champaign   **Award Amount: $1,590K**
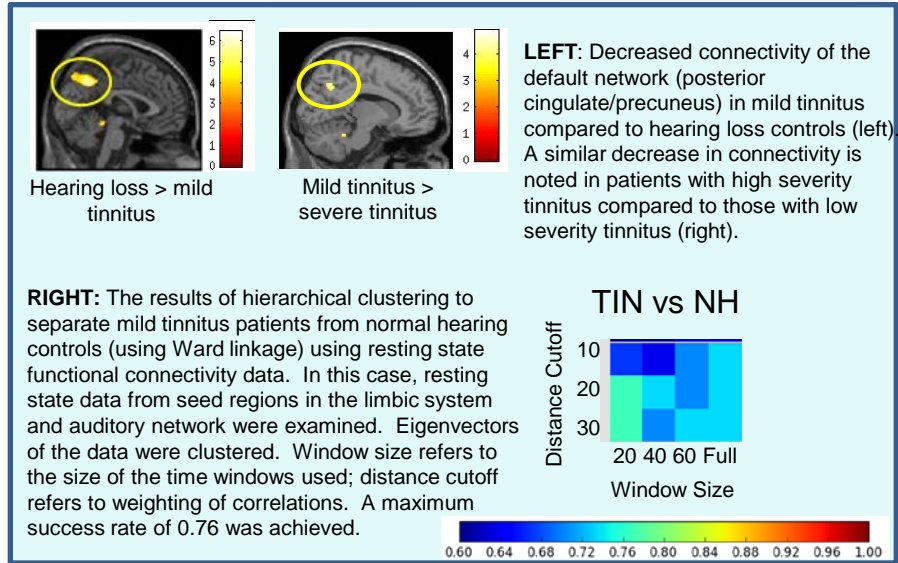
Study/Product Aim(s)

1. Identify functional biomarkers of tinnitus severity using resting state functional connectivity
2. Determine tinnitus subgroups using automated cluster analysis of resting state data and associate the subgroups with a set of behavioral and neural correlates

Approach

We plan to use resting state functional connectivity to identify neural correlates of tinnitus subgroups that differ in their tinnitus severity. We will assess the replicability of these measures by collecting this data in the same patients twice (1 week apart) and at two sites and in two populations (active duty service members vs civilians).

Additionally, we will use advanced topological data analysis and clustering tools to identify additional subgroups within our patient population, and correlate these subgroups with behavioral measures.

Hearing loss > mild tinnitus

Mild tinnitus > severe tinnitus

LEFT: Decreased connectivity of the default network (posterior cingulate/precuneus) in mild tinnitus compared to hearing loss controls (left). A similar decrease in connectivity is noted in patients with high severity tinnitus compared to those with low severity tinnitus (right).

RIGHT: The results of hierarchical clustering to separate mild tinnitus patients from normal hearing controls (using Ward linkage) using resting state functional connectivity data. In this case, resting state data from seed regions in the limbic system and auditory network were examined. Eigenvectors of the data were clustered. Window size refers to the size of the time windows used; distance cutoff refers to weighting of correlations. A maximum success rate of 0.76 was achieved.

TIN vs NH

Timeline and Cost

Activities CY	15	16	17
Protocol development/ IR approvals			
Patient recruitment and data collection			
Data analysis			
Report generation and dissemination			
Estimated Budget ($1,590K)	**$457**	**$569**	**$563**

Updated: (October 12, 2016)

Goals/Milestones

FY15
- Protocol development/IRB approval obtained at both sites
- Patient recruitment and data collection has begun at both sites

FY16
- Continue patient recruitment
- Data collection at both sites
- Ongoing data analysis
- Report(s) development, dissemination

FY17
- Completion of data collection at both sites
- Data analysis
- Report(s) development, dissemination