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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 at Urbana-Champaign

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The subject of the project is FY14 PRMRP Topic Area – Tinnitus. The broad goal 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 2, we had ongoing data collection using resting-state fMRI to identify characteristics of functional connectivity in attention, emotion, and auditory processing networks that are exclusive to the tinnitus population. We also used clustering algorithms applied to the resting-state data to differentiate patients with tinnitus from controls. We presented results in military and other conferences. In Year 3, we expect to complete data collection and analysis and submit manuscripts.

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

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1. INTRODUCTION:

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:

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

3. ACCOMPLISHMENTS:

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

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

        - Begin data collection
        - Number of total completed subjects expected:
            - UIUC: N = 20 patients and 10 controls
            - WHASC: N = 10 patients and 5 controls
        - For details on actual number of subjects on whom data has been collected, see next section.
        - *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.
            - Number of total completed subjects expected:
                - UIUC: N = 60 patients and 30 controls
                - WHASC: N = 40 patients and 20 controls
            - For year 2 (at end of first 24 months) details see next section.
        - Task 4: Behavioral and MRI data analysis:
            - Transfer HCE/WHASC data regularly to UIUC
            - Ongoing data processing and analysis to monitor data quality
            - For year 2 (at end of first 24 months) details see next section.

    - 24-36 months:
        - Task 5: Dissemination of results:
            - *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.**
    - 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
                - Percentage of completion at end of Year 2 (24 months): 100%
        - 18-36 months:
            - Task 2: Separate the tinnitus patient group and the control group into two groups
                - *Milestone to achieve:*
                    - Co-author paper on dissociating tinnitus from control groups based on blind, automated methods

- Percentage of completion at end of Year 2 (24 months): 50%

- Task 3: Cluster the larger tinnitus population into separate sub-groups based on imaging data; test for differences between civilian and military population
  - *Milestone to achieve:*
    - Co-author paper on the various subgroups of tinnitus based on brain imaging measures

- **What was accomplished under these goals?**

Accomplishments under these goals:

- **Specific Aim 1: Identify functional biomarkers of tinnitus severity using resting state functional connectivity.**
  - 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
        - 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.
        - Consultation with Dr. Tyler (from University of Iowa) via an in-person visit to modify research protocol was completed on November 11th, 2015.
        - 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.
        - IRB approval: 8/3/2015
        - HRPO approval: 9/21/2015
        - 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.
        - UIUC IRB protocol was successfully renewed on Jul 26, 2016 and information sent to HRPO.
      - IRB approval at WHASC
        - 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.
    - 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
    - MRI and behavioral protocols were finalized.
    - 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.
- Completion of Task 1: UIUC (9/21/2015), WHASC (9/9/2016). (Year 1)

- <u>Task 2: Participant recruitment, participant evaluation, MRI and behavioral data acquisition</u>

    - At UIUC, behavioral and MRI data collection has been ongoing.
    - Behavioral data collection at UIUC

        - By September 15th, 2017, behavioral data were collected on 124 human subjects, including 81 patients and 43 controls. 14 additional subjects have been contacted for initial screening. Recruitment and data collection are ongoing.

    - MRI data collection at UIUC

        - By September 15th, 2017, MRI data (both visits) were collected on 49 participants (35 patients, 14 controls). 15 additional subjects were in the process of being scheduled for MRI data collection.

    - Data collection at WHASC was delayed due to the move to a new facility and ongoing issues with the MRI scanner. The team moved into the new WHASC at the end of June and data collection was stopped due to calibration and inspection requirements that had to be completed prior to testing participants.

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

        - To date, the team has consented 36 participants of which 30 have been enrolled in the study. Four participants were not

eligible to enroll in the study, 1 participant was lost to follow-up, and 1 participant moved to another duty location. Data collection has been completed for 17 participants and the research team is currently working on completing data collection on the remaining 13 participants. As of September 2017, 8 patients and 9 controls have been consented and enrolled to participate, with data collection scheduled September – November 2017.

- MRI scanner has had continuing issues with the custom-made control box used for the biological measures. Additional boxes were created to help mitigate issues.
- Recruitment and data collection are ongoing.

- Task 3: Behavioral and MRI data analysis

  - Preliminary data analysis of 8 controls from UIUC, 6 controls from WHASC, 18 patients from UIUC and 7 patients from WHASC revealed that resting state functional connectivity within the auditory, dorsal attention, and default mode resting state networks was replicable in both groups at both sites. More control participants (in particular, those with hearing loss matched to that of the tinnitus group) are being collected to verify these results, and an analysis using intra-class correlation coefficients to assess replicability is underway.

    Further, more participants with bothersome tinnitus are being recruited. Currently, scores on the Tinnitus Functional Index (TFI) range from 3.6 to 58.8 at UIUC and from 11.2 to 48.4 at WHASC. There is some variation in TFI scores across the two MRI visits, with an average difference of -3.36 ±7.38 at UIUC and 3.37 ±8.33 at WHASC. Analysis thus far has suggested that small variations in connectivity across visit are not related to differences in TFI scores.

  - Preliminary data analysis of the behavioral results on 11 normal hearing tinnitus participants and 14 hearing-matched controls collected at UIUC suggests that speech-in-noise recognition ability was affected by tinnitus loudness measured with loudness matching, but not tinnitus severity. A manuscript discussing between-group speech-in-noise performance has been submitted for publication.

  - 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 20.35 dB HL for right ear (std. dev. =11.04 dB), and 21.34 for left ear (std. dev. = 11.21) with 3.75 dB HL as the lowest PTA and 76.25 dB HL as the highest. Analysis of control group

revealed mean pure tone average (PTA; average of pure tone frequencies 0.5, 1, 2, and 4 kHz) to be 12.8 HL for right ear (std. dev. =7.46 dB), and 12.2 for left ear (std. dev. = 7.02) with 1.25 HL as the lowest PTA and 41.3 dB HL as the highest. Additionally, scores on the Tinnitus Handicap Inventory (THI) for the tinnitus group ranged from 0 to 84 with a mean score of 19.39 (std. dev.= 14.64).

- Dr. Husain met with Dr. Sherman and Ms. Camou at end of August in Florida at the Military Health Systems Research Symposium and discussed ongoing progress and future plans.
- Dr. Husain is scheduled to meet with Dr. Esquivel at the NCRAR Tinnitus conference Oct 4-6 in Portland, Oregon
- Dr. Husain is scheduled to visit WHASC/HCE in February 2018 to review progress in data collection.

- **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 been completed.
  - 18-36 months:
    - Task 2: Separate the tinnitus patient group and the control group into two groups
      - Paper dissociating tinnitus from control groups based on blind, automated methods is in prep and will be submitted shortly.
      - Using the developed analysis method and clustering techniques, we have achieved a 78% classification rate. Efforts to improve this further are underway, including both alterations to the analysis protocol and inclusion of behavioral data in conjunction with fMRI data.

- **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 to disseminate research findings to communities of interest and to obtain feedback, for Year2 (September 15, 2016-September 14, 2017). Team members involved in the project presented results of their individual projects as posters or podium presentation at diverse venues. Dr. Husain gave a number of talks internationally and nationally for the purpose of disseminating the research findings and gathering feedback, before submission of papers. We are pleased to note that currently, we have one paper under review and another paper about to be submitted. For details about these products, please see section 6.

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

  The following activities were undertaken to disseminate research findings to communities of interest and to obtain feedback, for Year2 (September 15, 2016-September 14, 2017). Team members involved in the project presented results of their individual projects as posters or podium presentation at diverse venues. Dr. Husain gave a number of talks internationally and nationally for the purpose of disseminating the research findings and gathering feedback, before submission of papers. We are pleased to note that currently, we have one paper under review and another paper about to be submitted. For details about these products, please see section 6.

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

  The main goal for Year 3 is to complete data collection at both sites and to focus on completing data analyses and disseminating results in the form of journal articles and presentations. Data collection has progressed smoothly at UIUC; recruitment and scanning efforts are now focused on control participants with hearing profiles matched to tinnitus patients, as well as tinnitus patients with bothersome tinnitus.

  At WHASC data collection was halted during a move to a new facility and again following continued difficulty with the MRI scanner. Calibrations and inspections had to be completed prior to team testing participants in the new hospital. While most issues are resolved, solutions have been put into place so that data collection can proceed smoothly. The team is planning to expand their recruitment efforts to Brooke Army Medical Center (BAMC). The BAMC Audiology Clinic holds a monthly Progressive Tinnitus Management meeting and the Chief has approved recruitment from this group and their patient population (pending IRB approval). Recruitment was ongoing during the equipment problems, and there are 14 participants waiting to be scheduled.

  Preliminary analysis of the behavioral data at UIUC has been conducted on patients and controls with normal hearing sensitivity, and a manuscript that summarized the results is under review. Further analyses of behavioral data will be conducted while including gender, age, hearing sensitivity, and tinnitus severity measured by various tinnitus-related questionnaires as factors.

  Preliminary analysis of the replication of the fMRI data is progressing, and a manuscript summarizing our results thus far is currently in preparation. Aim #2 is also well underway, with the analysis protocol finalized and a paper summarizing our analysis methods and preliminary results nearly ready to be submitted for publication.

4. IMPACT:

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

  Nothing to Report.

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

  Nothing to Report.

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

  Nothing to Report.

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

  Nothing to Report.

5. CHANGES/PROBLEMS:

- **Changes in approach and reasons for change**
  - Nothing to Report at UIUC or at WHASC
- **Actual or anticipated problems or delays and actions or plans to resolve them**
  - We encountered unanticipated delays at WHASC.
    - All of WHASC moved to a new facility, requiring set-up of new equipment to meet study protocol needs, attending safety briefings and acquiring new access cards and keys.
      - The move also made recruitment difficult since new permissions and processes were developed to post recruitment flyers. Furthermore, the team is still having problems with the WHASC phone system because it is not fully operational and calls cannot be made or received frequently.
    - The MRI was intermittently down following issues with the control box for the biological measures. The UIUC has provided a new control box and issues have been resolved.
    - Due to factors beyond WHASC's control, the Radiology Department changed available scanning times from Tuesdays to Mondays. The official start date of this change was finally set on September 25, 2017.
    - The team will be recruiting from the BAMC Audiology Clinic and their PTM monthly meeting attendees.
- **Changes that had a significant impact on expenditures**

  Nothing to Report.

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

Nothing to Report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

  - **Journal publications.**

    1. Tai, Y. & Husain, F. T. (2017). *Right-ear advantage for speech-in-noise recognition in patients with non-lateralized tinnitus and normal hearing sensitivity.* Manuscript under 2nd review.

    2. Zimmerman, B., Abraham, I., Schmidt, S.A., Baryshnikov, Y., & Husain, F.T. (in preparation) *Dissociating tinnitus patients from healthy controls using resting state cyclicity analysis and clustering.*

  - **Books or other non-periodical, one-time publications.**

    Nothing to Report.

  - **Other publications, conference papers, and presentations.**

    Poster presentations

    1. Schmidt, S. A., Tai, Y., Zimmerman, B., Husain, F.T. (2017) *Resting state networks of tinnitus patients are replicable: a preliminary study.* Association for Research in Otolaryngology 40th Midwinter Meeting, Baltimore, MD, February 11-15, 2017.

    2. Tai, Y., Tsao, A. L., Husain, F. T. (2017). *Effect of tinnitus severity and loudness on speech-in-noise ability in normal hearing tinnitus patients*. Association for Research in Otolaryngology 40th Midwinter Meeting, Baltimore, MD, February 11-15, 2017.

    3. Husain, F.T., Zimmerman, B., Schmidt, S. A., Thomas, I., Baryshnikov, Y. (2017). *Using novel mathematical technique to classify tinnitus patients and differentiate them from controls*. Military Health System Research Symposium (MHSRS), Kissimmee, FL, August 27-30, 2017.

    4. Tai, Y., Husain, F. T. (2017, accepted). *Does tinnitus affect speech-in-noise recognition in patients with normal hearing?* National Center for Rehabilitative Auditory Research (NCRAR) Conference, Portland, OR, October 4-6, 2017.

    5. Tai, Y., Tsao, A. L., Tyler, R. S., Husain, F. T. (2017, accepted). *Speech-in-noise recognition in normal hearing threshold tinnitus patients.* American Speech-Language-Hearing Association convention, Los Angeles, CA, November 9-11, 2017.

    Talks or podium presentations

    1. Husain, F.T. (2016). *Tinnitus heterogeneity: Neural correlates from rest and task based fMRI*. Seminar Series, Institute on Neuroscience, Newcastle University, UK, November 2, 2016.

2. Husain, F.T. (2016). *Tinnitus heterogeneity: Neural correlates from rest and task based fMRI.* ENT Seminar series, University Medical Center Groningen, Groningen, Netherlands, December 9, 2016.

3. Schmidt, S.A**.**, Husain, F.T. (2017). *Resting state and the default mode in tinnitus.* Ear Day, Department of Communication Disorders and Sciences, Rush University and Chicago Chapter of the Acoustical Society of America, Chicago, IL, January 27, 2017.

4. Husain, F.T. (2017). *Understanding the Effect of Tinnitus on Auditory and Extra-Auditory Neural Networks.* Ear Day, Department of Communication Disorders and Sciences, Rush University and Chicago Chapter of the Acoustical Society of America, Chicago, IL, January 27, 2017.

5. Husain, F.T. (2017). *Using resting state functional connectivity to investigate neural correlates of tinnitus.* NIDCD Seminar, National Institutes of Health, Bethesda, MD, February 15, 2017.

6. Husain, F.T. (2017). *Neural networks of tinnitus in humans: Elucidating severity and habituation*, Hearing and Balance 2017 conference, Sao Paulo, Brazil, April 6-8, 2017.

7. Esquivel, C.R., Levy, C., Schmidt, S.A., Husain, F.T. (2017). *Identifying Subgroups of Tinnitus Using Novel Resting fMRI Biomarkers and Cluster Analysis,* Collaborative Auditory Vestibular Research Network, San Antonio, TX, June 14, 2017.

8. Husain, F. T., Schmidt, S, A., Esquivel, C. R., Sherman, P. M. (2017). *Towards developing reliable, objective biomarkers of tinnitus using resting state fMRI*. Podium presentation at the Military Health System Research Symposium (MHSRS), Kissimmee, Florida, August 27-30, 2017.

9. Husain, F.T. (2017). *Auditory and extra-auditory networks implicated in tinnitus: evidence from fMRI studies.* International Symposium on Hearing Loss and Tinnitus – Celebrating the Work of Jos J. Eggermont, pre-conference meeting for International Auditory Cortex Conference, Banff, Canada, September 10, 2017.

10. Husain, F.T. (2017). *Neuroplasticity in tinnitus: evidence from resting state FMRI studies*. Eight AFREPA (Association Française des Équipes Pluridisciplinaires en Acouphènologie) conference, Lyon, France, September 15-16, 2017.

- **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?**

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. She is overseeing the MRI data collection at UIUC, performed preliminary data analysis and is drafting a paper summarizing the fMRI replicability results.*

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: *Dr. 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: *Shraddha Shende, MA*
Project Role: *Graduate Student*
Research Identifier: *orcid.org/ 0000-0001-9844-7078*
Nearest person month worked*: 0.75*
Contribution to Project: *Ms. Shende has helped coordinate recruitments for potential participants. She also conducted the behavioral testing for the current project. Took over Anthony Tsao's position after August 16, 2017.*

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. Ended his work on the grant due to starting his AuD 4th year externship by May 16, 2017.*

Name: *Rafay Khan*
Project Role: *Graduate Student*
Research Identifier: *orcid.org/ 0000-0002-6146-5800*
Nearest person month worked*: 1.0*
Contribution to Project: *Mr. Khan is assisting with data collection at UIUC and is beginning work on analysis of white matter structural data collected at UIUC. He started working on the project on August 16, 2017.*

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 is supervising 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 is facilitating 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) is 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) is 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 is in charge of behavioral data collection at WHASC and also assists with MRI data collection. She is also responsible for transferring data from WHASC to UIUC.*

- **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

- **COLLABORATIVE AWARDS:**

  Not applicable.

- **QUAD CHARTS:**

  See attached.

9. 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**

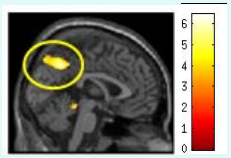
Study/Product Aim(s)

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.

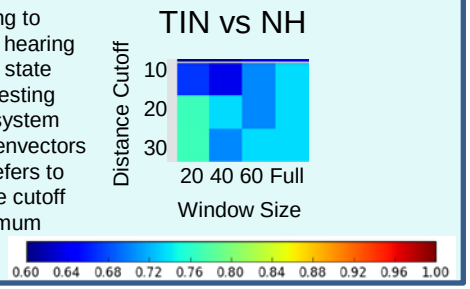


Hearing loss > mild tinnitus

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.



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 13, 2017)

Goals/Milestones

FY15
- Protocol development/IRB approval obtained
- Began patient recruitment and data collection

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