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TITLE: Quantitative Evaluation of Visual and Auditory Dysfunction and Multi-Sensory Integration in Complex TBI Patients

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14. ABSTRACT
The majority of moderate and mild TBI (mTBI) patients report self-described visual and/or auditory (i.e. sensory) dysfunction and yet they often pass standard eye and hearing exams. Further, 80% of TBI patients are diagnosed as mTBI and appear normal on a standard CT or MRI scan. Due to the inherent variability of trauma, no single trauma case is exactly like another. This variability in combination with the lack of profound damage in mTBI patients in particular has made diagnosis of these patients challenging. The lack of an objective quantitative clinical metric for these changes in sensory function also prevents the initiation of clinical trials. Further, it highlights the lack of understanding of the underlying cause of the sensory dysfunction. Without an understanding of mechanism, rational therapies cannot be developed. The goals of this study are to identify sensitive, objective, quantitative tests to serve as diagnostics and outcome measures for sensory dysfunction in TBI patients and to better understand the physiological basis of sensory dysfunction. We propose that by assessing TBI patients in a Level 1 Trauma Center, two Veterans Administration Hospitals, and a military base that houses a satellite of the National Intrepid Center of Excellence. We will recruit sufficient numbers of subjects to definitively identify assessments that are sensitive and specific enough to diagnose sensory dysfunction in complex TBI patients. We hypothesize that combining objective structural and functional assessments in the same subjects is more likely to overcome the inherent variability of trauma and yield useful diagnostic metrics

15. SUBJECT TERMS
mild traumatic brain injury (mTBI); visual dysfunction; auditory dysfunction; magnetic resonance imaging (MRI); electroencephalogram (EEG); sensory integration

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1. INTRODUCTION: The majority of moderate and mild TBI (mTBI) patients report self-described visual and/or auditory (i.e. sensory) dysfunction and yet they often pass standard eye and hearing exams. Further, 80% of TBI patients are diagnosed as mTBI and appear normal on a standard CT or MRI scan. Due to the inherent variability of trauma, no single trauma case is exactly like another. This variability in combination with the lack of profound damage in mTBI patients in particular has made diagnosis of these patients challenging. The lack of an objective quantitative clinical metric for these changes in sensory function also prevents the initiation of clinical trials. Further, it highlights the lack of understanding of the underlying cause of the sensory dysfunction. Without an understanding of mechanism, rational therapies cannot be developed. The goals of this study are to identify sensitive, objective, quantitative tests to serve as diagnostics and outcome measures for sensory dysfunction in TBI patients and to better understand the physiological basis of sensory dysfunction. We propose that by assessing TBI patients in a Level 1 Trauma Center, two Veterans Administration Hospitals, and a military base that houses a satellite of the National Intrepid Center of Excellence. We will recruit sufficient numbers of subjects to definitively identify assessments that are sensitive and specific enough to diagnose sensory dysfunction in complex TBI patients. We hypothesize that combining objective structural and functional assessments in the same subjects is more likely to overcome the inherent variability of trauma and yield useful diagnostic metrics than would each test separately. Thus, we propose that a combination of assessments including a single metric that indexes integrative sensory abilities, and utilization of new, sensitive algorithms may be required for accurate diagnosis.

2. KEYWORDS:
mild traumatic brain injury (mTBI); visual dysfunction; auditory dysfunction; magnetic resonance imaging (MRI); electroencephalogram (EEG); sensory integration

3. ACCOMPLISHMENTS:
What were the major goals of the project?
Specific Aim 1: **To derive a combination of objective and quantitative metrics to diagnose visual and/or auditory dysfunction after TBI.** We will test the working hypothesis that our newly derived diagnostic battery is more sensitive and accurate than any single assessment alone.

Specific Aim 2: **To identify and track alterations in the brain that underlies self-reported sensory deficits after TBI.** We will test the working hypothesis that visual and auditory dysfunction after TBI is due to brain-level damage that is detectable with our sensitive, newly developed algorithms.

Specific Aim 3: To identify deficits in multi-sensory integration and the cortical correlates of these deficits in complex TBI patients. We will test the working hypothesis that alterations within each sensory modality result in combinatorial changes in multisensory integration that can be indexed to yield a sensitive, quantitative diagnostic of complex TBI due to sensory dysfunction.

Major Tasks:
1. Obtain IRB and HRPO approvals at all sites
2. Coordinate study staff
3. Recruit, enroll and screen potential subjects
4. Perform ophthalmic exams
5. Perform audiological exams
6. Perform EEGs, including evoked potentials and sensory integration tasks
7. Perform MRIs
8. Analyze data

What was accomplished under these goals?
1) Major Activities:

A. We hired a clinical study coordinator who is also an ophthalmic technician. We had her trained on measuring accommodation and convergence by the Vanderbilt Eye Institute orthoptist, Ronald Biernacki, CO.

She performs the majority of the ophthalmic exam with the exception of the fundus exam, which is performed by one of the Ophthalmologists on the study. She also obtained VA clearance so that she can access potential subjects at TVHCS.

We also recruited two post-baccalaureates who are working on the project full-time, assisting with recruitment, consent, and EEG. Finally, we have two undergraduate researchers working on the project part-time. They are assisting with recruitment and performing and analyzing the EEGs.

B. We obtained IRB approval at VUMC in the Fall of 2017. We then obtained IRB approval at TVHCS in January of 2018. Recruitment was then initiated at these sites. We met with the VUMC rehabilitation center, which agreed to assist with recruitment. We also met with the TVHCS Trauma coordinator who is assisting us with recruitment of Veterans. Finally, we send out emails via Research Match, which has been very effective.

C. In the interim from submitting our grant proposal and being selected for funding, Fort Campbell was changed from a research military base to a clinical only (non-research) base. As a result, we had to apply for an exemption. Dr. Groves navigated this process successfully and we again received approval from Blanchfield Hospital Command. In addition, the DoD was in the midst of reorganizing the IRBs/HRPOs for the military bases such that it was unclear which office we now needed to go through in order to obtain regulatory approval. We were deferred to US Army headquarters who agreed to defer to the VUMC IRB. The VUMC IRB agreed to be the primary site and thus we converted our IRB to a single IRB that would encompass both sites. However, we were then informed that while MEDCOM headquarters had a DoD-wide Assurance, they did not currently have an institutional official who could sign off on an Institutional Agreement or Individual Investigator Agreement. The MEDCOM headquarters AHRPO representative then requested to the VUMC IRB that they take on the responsibility of the Individual Investigator by signing the associated agreement. However, VUMC refused to take on the liability of the DoD investigators. Dr. Zola then navigated the system and identified an individual at the DoD who had set up other multi-site studies that included Fort Campbell and we able to obtain DoD Individual Investigator Assurance for the investigators at Fort Campbell. This finally occurred in April, 2018. Additional CITI training was required from some of the investigators and some of the language in the VUMC documents had to be altered to be appropriate and acceptable for Fort Campbell. There was a further delay on this point due to a lack of understanding by the VUMC IRB and the fact that they moved offices. However, we have finally overcome all of these barriers and just received IRB approval for Fort Campbell as of October 2nd. We are now submitting the paperwork to the DoD HRPO for final approval and will then be able to initiate the study at Fort Campbell.

D. We were provided a lane in the VEI that has all of the equipment and space needed for the ophthalmic exam.

E. Ms. Miller traveled to Fort Campbell and met with the Ophthalmology team there. During that visit she confirmed that the ophthalmic exam could be performed at their site as it is being done at VUMC.

F. We have added Audiologists to our team both at VUMC and at Fort Campbell: Drs. Linda Hood, Rene Gifford, and Kara Bean. They have added important assessments of the audiological system that include electrophysiology and speech. We are now assessing the entire system from ear to cortex. Dr. Bean, the audiologist at Fort Campbell traveled to VUMC for training on some of the assessments that we will perform. In addition, Drs. Hood and Gifford traveled to Fort Campbell to assure consistency and communication across sites.

G. We performed initial testing of the ability of the Fort Campbell Intrepid Center EEG system to be able to accurately provide stimuli and measure responses for the sensory integration tasks performed in the EEG framework. Unfortunately the system is entirely passive and is thus unable to be used for the evoked potentials or the sensory integration tasks. We identified two systems that fit in our budget and had the potential to perform the necessary assessments. Representatives visited and performed demonstrations where we tested the ability of the systems to accurately time-stamp and communicate with the amplifier. Weeks later we finally received the data that was collected and were able to analyze it. Fortunately, one system will work well and we have ordered it. It is expected to arrive within a month. We will then have training, the protocols will be uploaded on the associated computer, and the system will be housed at the Intrepid Center for the duration of the study.

H. Dr. Zola required an updated version of Neuroguide software for analysis of the resting-state EEG data. We have purchased that for him.

I. The Vanderbilt University Institute of Imaging Science (VUIIS) has taken one MRI scanner off-line for several months for needed updates. This has led to all investigators utilizing a single MRI scanner and, of course, a long lead-time to access the scanner. As a result, even though we received IRB approval at the end of January and were able to identify interested potential subjects in March, we could not schedule them on the scanner until May.

J. Dr. Logan wanted to wait for IRB clearance before discussing with radiology regarding access to the MRI. However, in December, 2017 he began conversations with the Radiology Chief who stated that they required GE applications training for DTI. GE spoke with them by phone and we initiated conversations between Fort Campbell Radiology and Dr. Anderson, at VUIIS. We made multiple trips to Fort Campbell to meet the new Radiology Chief, explain the study and obtain approval for access to the scanner, which we did. We have made two additional trips to test our study protocol on their scanner. In the last visit the test went smoothly and successfully and we have scanned the same individual in the VUIIS MRI. Analytical comparisons of the two scans are now underway by Dr. Landman's laboratory.

2) Specific Objectives:

A. To continue enrolling and assessing subjects at VUMC and to begin data analysis.

B. To increase enrollment from TVHCS.

C. To initiate the study at Fort Campbell.

3) Significant Results:

A. Enrollment: We have performed the study on 11 subjects to date. We have an additional 20 subjects scheduled. We are currently scheduling an additional 50 potential subjects.

B. Ophthalmology: We have data from three TBI subjects and 7 controls to-date. Within this sample we have detected no differences in best-corrected visual acuity (BCVA), with all subjects presenting at 20/20 (data not shown). In addition, there were no differences between groups in pupil diameter (**Fig. 1A**), Ishihara color plates (data not shown), horizontal or vertical pursuits or saccades (data not shown), or intraocular pressure (**Fig. 1B**). Further, the eyes appeared normal on fundus exam. The lack of difference on these exams was expected and fits our hypothesis.

In contrast, we have already started to detect differences between TBI and control subjects in other ophthalmological exams as was anticipated based on previous studies. We are detecting differences in convergence (**Fig. 2A**) and accommodation (**Fig. 2B,C**). In addition, we are detecting differences in visual field mean deviation (**Fig. 3**), both at the individual and average level.

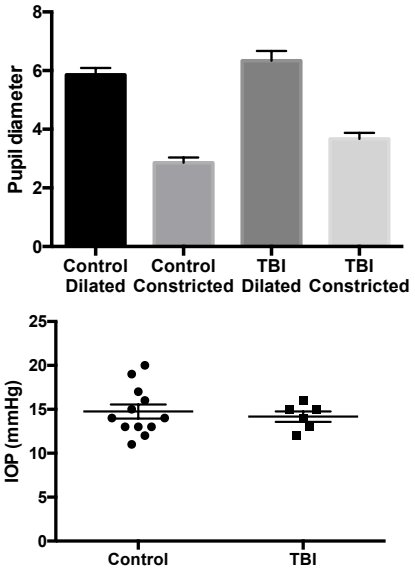


Figure 1. No differences between groups in standard ophthalmic exams. A) Pupil diameter. B) IOP.

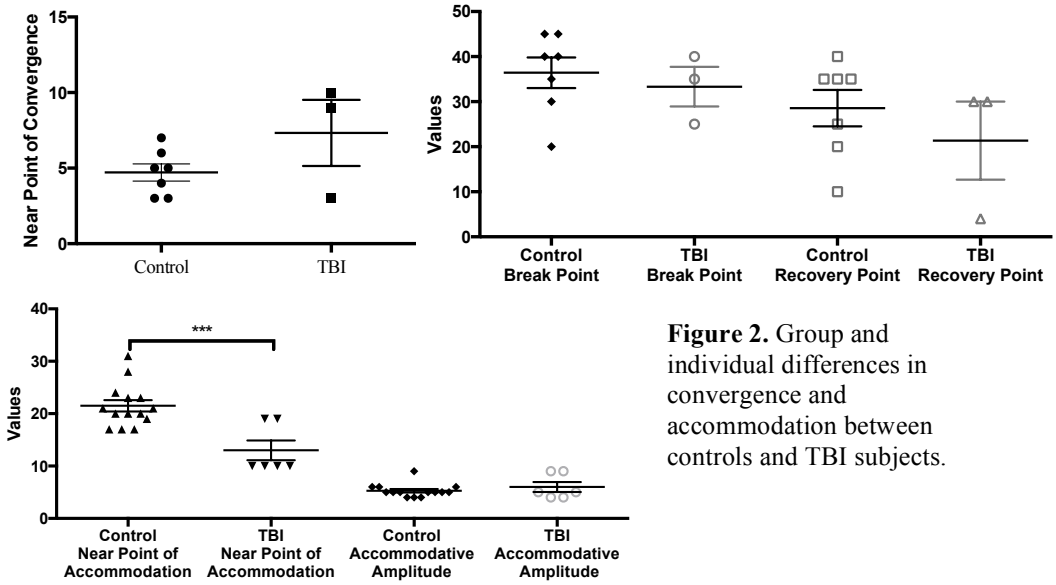


Figure 2. Group and individual differences in convergence and accommodation between controls and TBI subjects.

We are also imaging the retina using optical coherence tomography (OCT) and imaging the orbit, optic nerve, and visual pathways using MRI. We are just starting to analyze the OCT data, which we are collecting around the central retina and the optic nerve. Here we show a

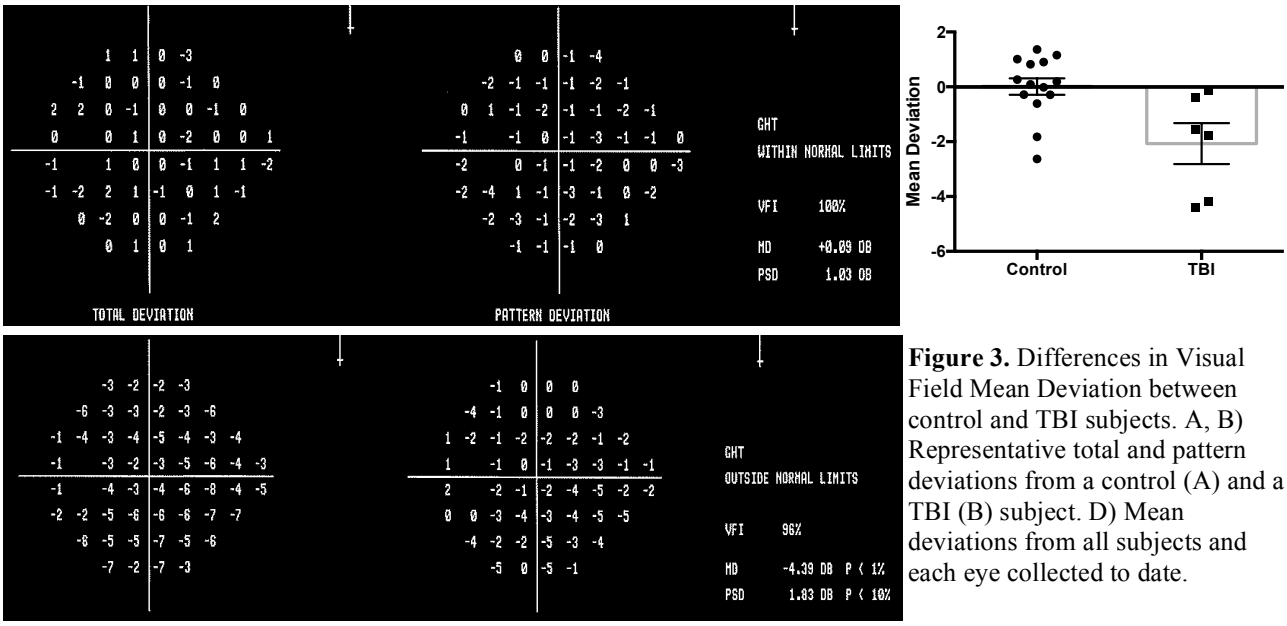


Figure 3. Differences in Visual Field Mean Deviation between control and TBI subjects. A, B) Representative total and pattern deviations from a control (A) and a TBI (B) subject. D) Mean deviations from all subjects and each eye collected to date.

representative image and quantification of retina thickness in a single control and a single TBI subject showing differences (**Fig. 4A,B**). We also show a representative MRI scan of the orbit and optic nerve (**Fig. 4C**). We are

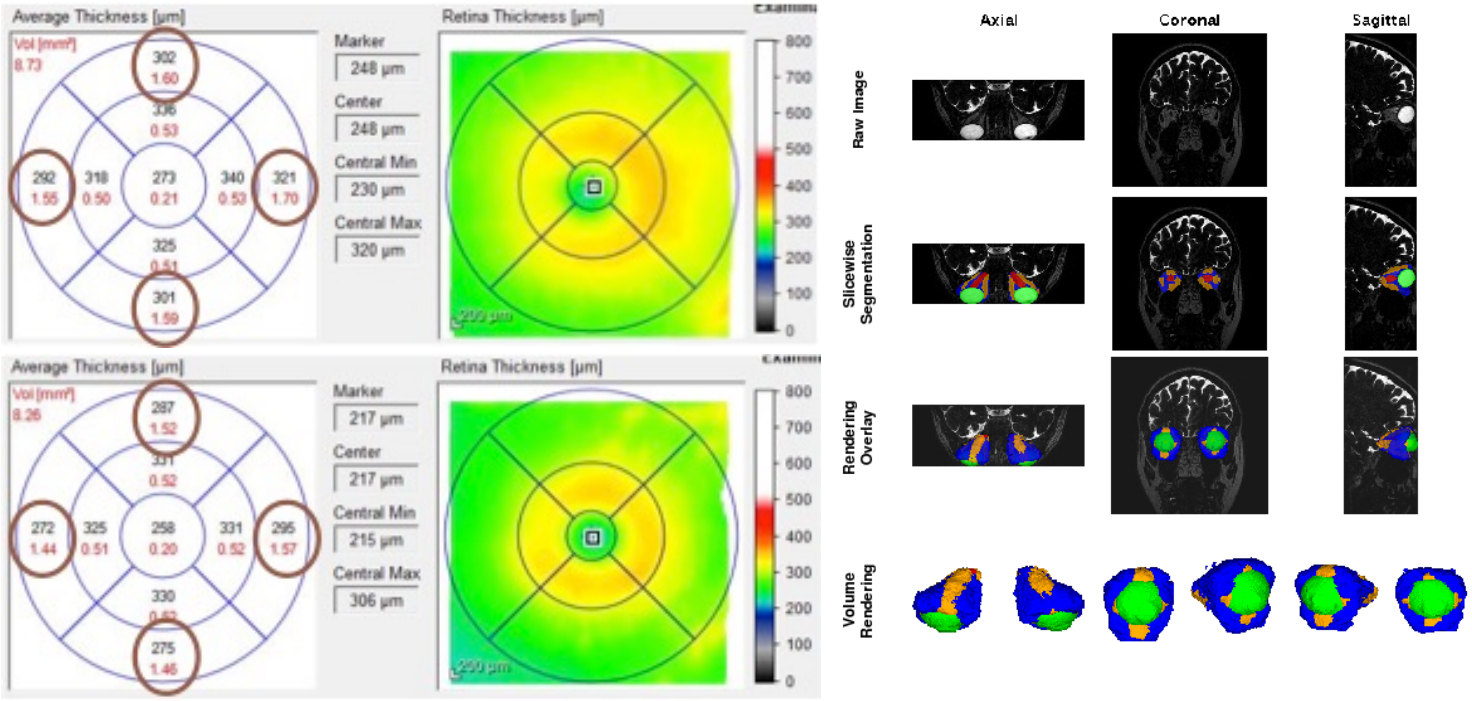


Figure 4. Imaging of the orbit, retina, and optic nerve. A,B) Heat maps and quantification of OCT images of the central retina. Red circles indicate areas of different retinal thicknesses between a control (A) and a TBI (B) subject. C) MRI of the orbit and optic nerve and segmentation of orbital fat (blue) and muscle (yellow) and optic nerve (red).

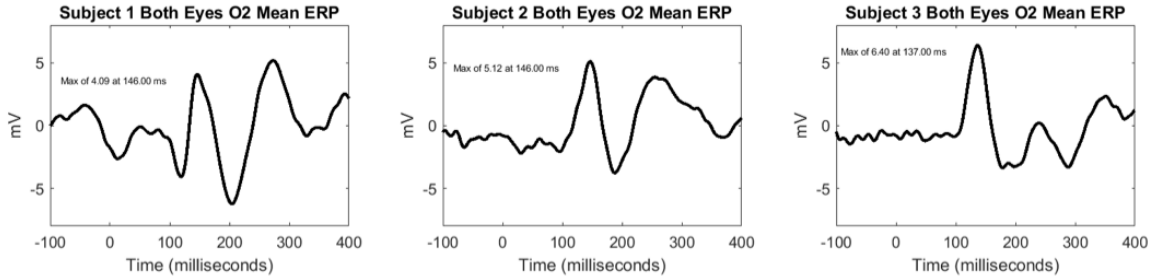


Figure 5. Visual Evoked Potentials. Representative VEPs from three control subjects.

in the process of quantifying parameters of these tissues with the goal of identifying changes that may explain the deficits identified in the visual fields. Finally, we show representative visual evoked potentials (VEP). We are

collecting data from each eye separately as well as both together (**Fig. 5**). We have also performed our study protocol on a single individual at both Fort Campbell and VUIIS and are performing the analysis now to determine similarities and differences between systems.

C. Audiology: We have added the following assessments to the already planned pure tone test and cortical auditory evoked potentials: auditory brainstem response (ABR), acoustic reflex thresholds, acoustic reflex delay, middle ear reflex, sound in noise, and distortion product otoacoustic emssions (DPOAE). Deficits in DPOAE and detection of central auditory processing disorder (which our combination of tests will detect) were reported in a study of 37 injured Veterans (Oleksiak et al., JRRD 2012). As expected, all TBI subjects tested in our study so far pass the standard audiological exams including the pure tone test (data not shown).

In contrast, we detect differences between TBI and control subjects in some clinical audiological assessments that are typically not performed clinically due to time and cost. The first example is the middle ear muscle reflex. The muscle reflex is designed to protect the auditory system from loud noises. If the reflex does not work appropriately, it would indicate damage to the muscle and a susceptibility of these patients to additional damage if exposed to high noise. In controls, the values were around the historical control average of 85 dB HL. However, in the TBI subjects the values were typically 90 dB HL or higher (**Fig. 6A**). Many TBI patients report difficulty hearing in loud environments. Therefore, we expected to detect deficits in the sound in noise (QuickSIN) task. We detected hearing deficits in 3 of 6 ears measured (**Fig. 6C**). In addition, we detect a decrease in the average amplitude of Wave I of the Auditory Evoked Potential, and a trend for significance in the Wave V amplitude (**Fig. 6B**). Additional analyses of these wave-forms are ongoing. We had expected that there would be no difference between groups in the air conduction thresholds at normally tested frequencies (up to 6kHz), and that is what we have found so far (**Fig. 7A**). In contrast we expected to detect differences in the air conduction thresholds at high frequencies (9kHz-16kHz; **Fig. 7B**). Right now, the average data is similar between the groups. However, it is important to note that the values in our control group are outside of the normal range

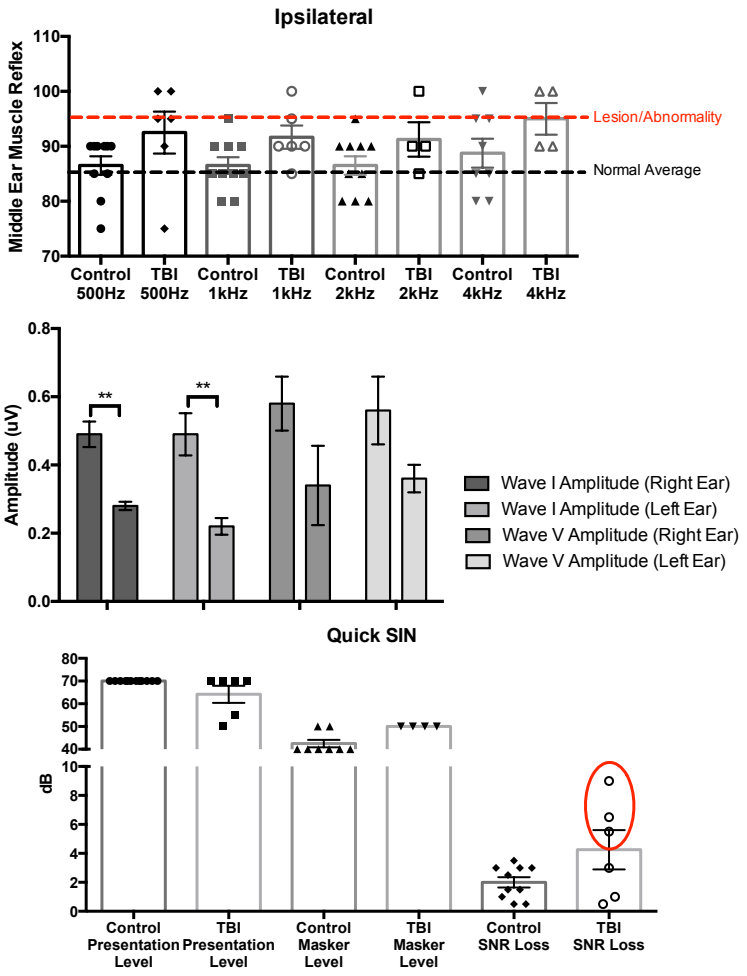


Figure 6. Alterations in the Auditory Pathway. A) Deficits in the middle ear reflex in TBI subjects. B) Decreased amplitudes in the Auditory Evoked Potential. C) Measurement of ability to hear sound in noise (SIN). Red circle indicates values representative of moderate hearing loss.

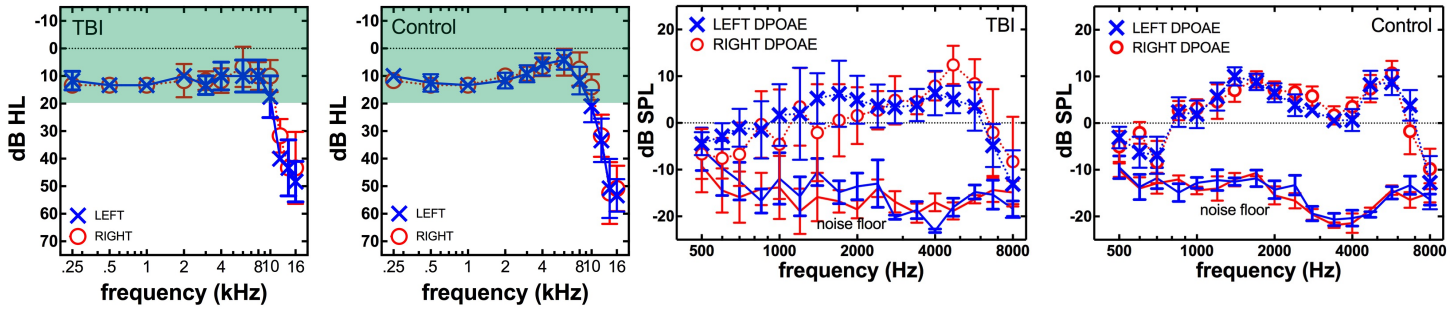


Figure 7. Air Conduction Thresholds in: A) TBI subjects, B) control subjects. **DPOAE amplitudes** in: C) TBI subjects, D) control subjects.

based on historical data and previous publications suggesting that our controls to-date are not entirely normal. The DPOAEs appear different between the controls and some of the TBI subjects (**Fig. 7C,D**). We are currently performing the analysis to determine if the amplitudes are in fact significantly different from controls. This is interesting from a clinical perspective because clinical audiologists look for presence or absence of emission, they do not assess differences in amplitudes, and thus they could be missing an important clinical finding for TBI patients.

D. MRI: We have detected potential microbleeds in the TBI subjects, but not the controls. An example of a microbleed in a TBI subject is shown in Fig. 8. The regions of the microbleeds vary considerably and may be due to the mechanism of injury – this is something we plan to analyze. In this particular subject it is located in the right posterior occipital/parietal cortex as indicated by the green arrow (**Fig. 8**).

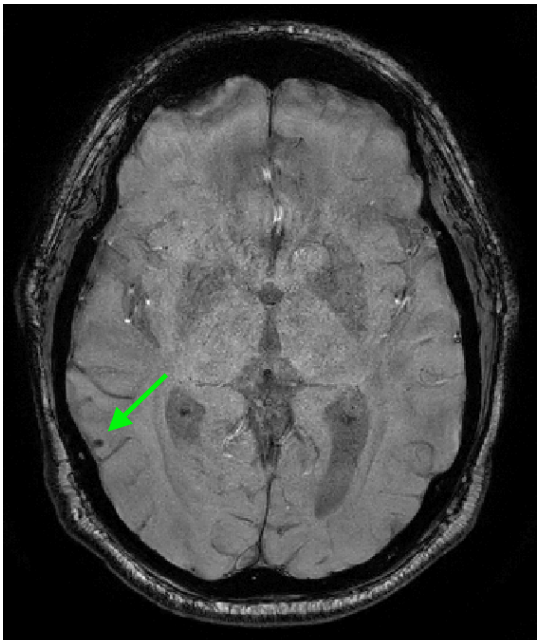


Figure 8. Microbleeds detected by MRI. The green arrow indicates a microbleed in a TBI subject.

We have made preliminary measurements of the volume, area, and length of a few representative areas within the visual and auditory pathways (**Fig. 9**). As expected, we do not detect gross differences in size. We are in the process of analyzing the MRI data including spider statistics on brain topology, DTI, fMRI, brain volume and atlas brain segmentation, optic nerve segmentation, sucal depth, and cortical shape. Some examples of these analyses on a control subject are shown (**Figs. 10-12**). We will also perform visual and auditory pathway analysis.

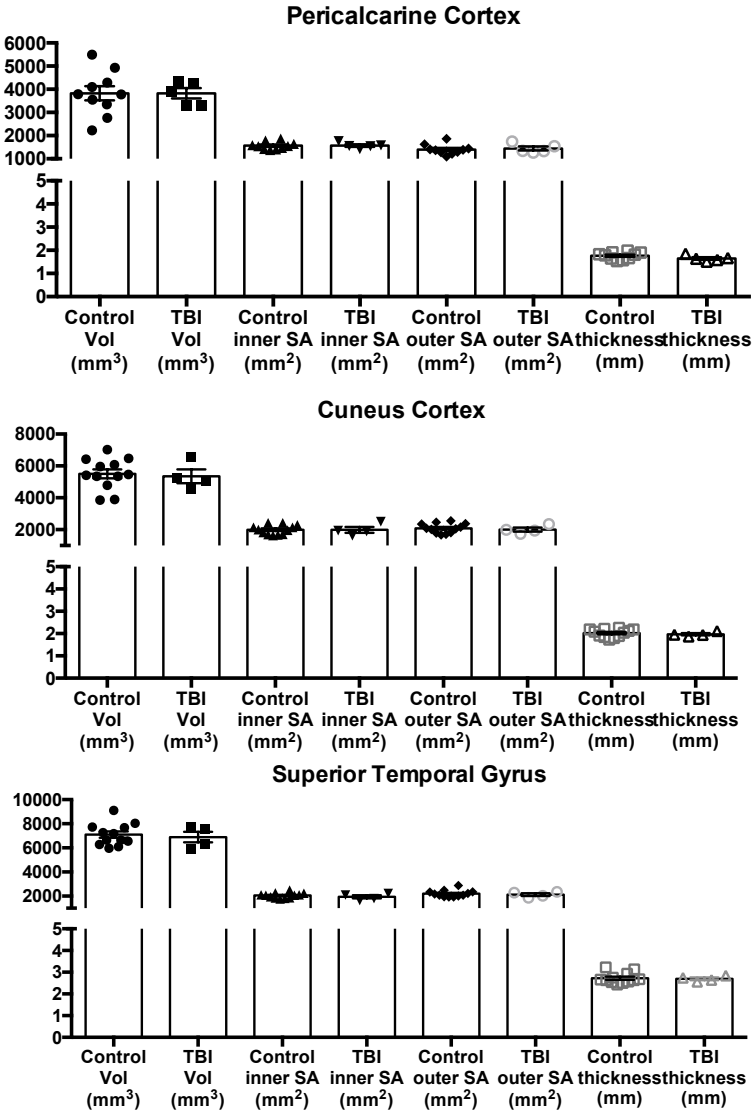


Figure 9. Quantification of volume, area, and length of some visual (pericalcarine cortex (A) and cuneus cortex (B)) and auditory (superior temporal gyrus (C)) areas. As expected, no gross abnormalities have been detected.

4) Other Achievements:
None to report.

What opportunities for training and professional development has the project provided?
Nothing to Report

How were the results disseminated to communities of interest?
I have presented seminars to the VUMC Neurology Grand Rounds, and the VUIIS, and I presented a poster at a VEI poster session describing the rationale and design of the study. Once we have substantial results we will present at national/international conferences.

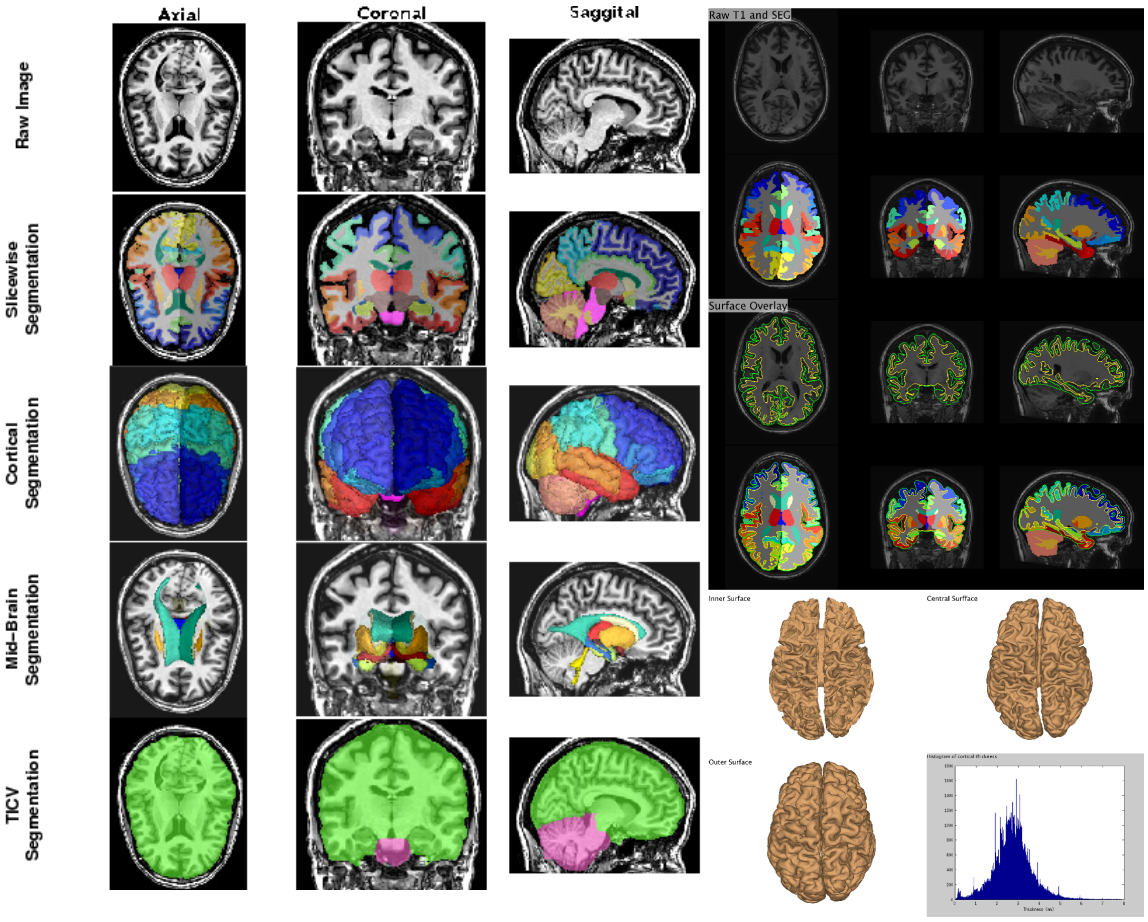


Figure 10. Whole Brain multi-atlas segmentation and cortical reconstruction.

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

We have identified additional clinics at VUMC and TVHCS that have agreed to advertise our study and we have provided them materials. We will continue to follow up with them and the existing clinics. We will also initiate the study at Fort Campbell beginning with obtaining HRPO approval and holding a PI meeting to organize that site. We will

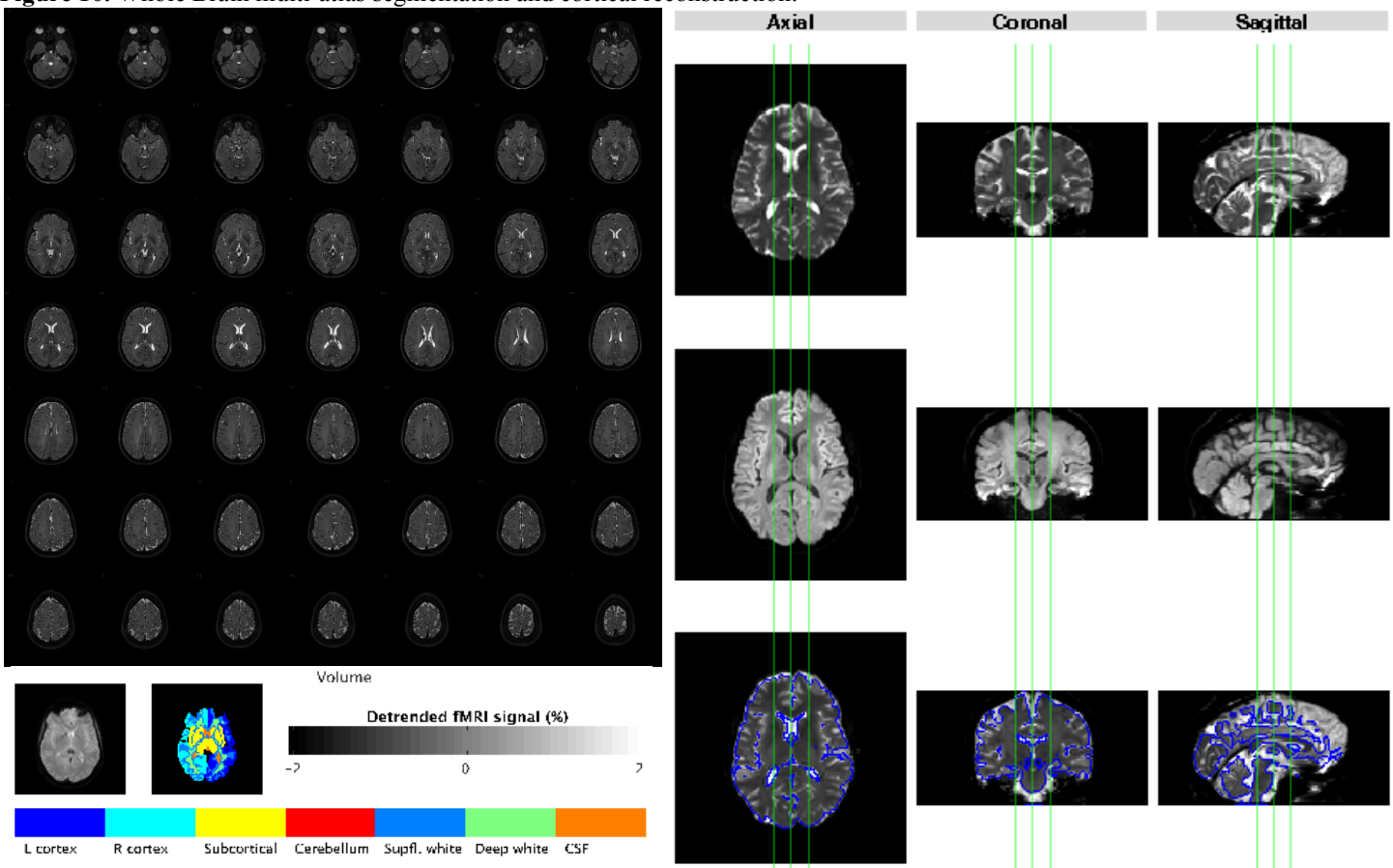


Figure 11. Examples of preliminary, level 1 MRI analyses in a control subject. A. FLAIR, B. fMRI, C.DTI.

obtain the new EEG system for Fort Campbell and schedule training as soon as possible. Finally, we will continue examining subjects as they are identified and will analyze the data and post it on FITBIR annually according to the new guidelines.

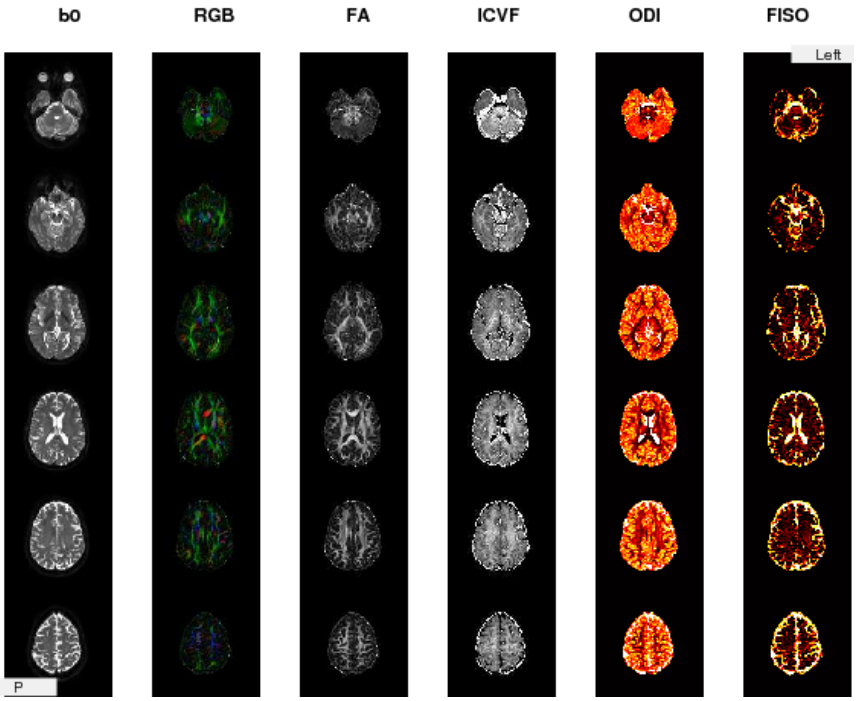


Figure 12. Examples of preliminary MRI analysis in a control subject.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?
None to date as the study is in preliminary stages.

What was the impact on other disciplines?
None to date as the study is in preliminary stages.

What was the impact on technology transfer?
None to date.

What was the impact on society beyond science and technology?
Nothing to Report.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change:
We added Audiologists and a more comprehensive audiological exam to the study. This was done due to literature in other areas suggesting that patients may experience synaptic damage in the audiological pathway between the ear and the cortex (subcortical damage) that would have been missed without these assessments. The methods and analyses are highly specialized and involved and therefore required the addition of these experts. This makes the study more complete and robust and now the ophthalmological and audiological studies are more balanced. We will now truly be studying both systems from the peripheral site of sensory reception to the cortex, including sites of audio-visual integration.

Actual or anticipated problems or delays and actions or plans to resolve them:
As described in detail above, for a number of reasons outside of our control it has taken until Oct. 2nd, 2018 to obtain IRB approval for Fort Campbell. The paperwork is now being submitted for HRPO approval. Since we worked closely with MEDCOM headquarters AHRPO during the process we do not anticipate any problems with approval.

One of the two MRI scanners at VUIIS is down for service and is supposed to come back on-line before the end of the year. This has caused long lead-times as all investigators are now forced onto one scanner. This has slowed down the number of subjects we could assess. Once the other MRI is back on-line we expect to have greater access to the scanner and to be able to schedule subjects at a higher frequency.

Changes that had a significant impact on expenditures:
Due to the delay in obtaining regulatory approvals and the slow scheduling of subjects because of the challenges of getting access to the single MRI scanner that is currently available at VUMC, our costs this year have been substantially lower than expected. An additional reason for the lower expenditures was that we did not purchase another Deymed EEG system for the Fort Campbell site. Upon performing initial tests it became

apparent that the Deymed EEG system at the Fort Campbell Intrepid Center would not be able to perform and record the evoked potentials and sensory integration tasks as needed for the study. Therefore, we are purchasing a slightly more expensive system (Neuroscan) that has all of the functionality that we will need. The system has been ordered but has not been received and therefore the charges are not yet showing up on our account. We fully expect that expenditures will increase substantially very soon as the MRI scanner is up and running again and we add compensation for members of the Audiology team. We are providing some salary to a staff member to offset cost associated with performing the assessments and analyzing the resulting data, but additional support will likely be needed.

Significant changes in use or care of human subjects:

We have added audiological assessments. They are all non-invasive and have been approved by the VUMC IRB and DoD HRPO.

6. PRODUCTS:

Publications, conference papers, and presentations:

I have presented seminars to the VUMC Neurology Grand Rounds, and the VUIIS, and I presented a poster at a VEI poster session. Once we have substantial results we will present at national/international conferences.

Website or other internet site:

Nothing to Report

Technologies or techniques:

Nothing to Report

Inventions, patent applications, and/or licenses:

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS:

What individuals have worked on the project?

Name:	Tonia S. Rex
Project Role:	PI
Researcher Identifier (ORCID ID):	0000-0002-2566-8723
Nearest person month worked:	2.4
Contribution to Project:	Designed and organized study, hired personnel, navigated regulatory compliance and issues, supervised all activities, trained team members, published and presented research.
Funding Support:	NIH R01 EY022349; NIH U24 EY029893; DoD W81XWH-15-1-0559

Name:	Patrick Lavin
Project Role:	Co-PI
Researcher Identifier (ORCID ID):	N/A
Nearest person month worked:	0.6
Contribution to Project:	Assisted with design of ophthalmic exam and performs the fundus exam on all subjects seen at VUMC.
Funding Support:	N/A

Name:	Amy Chomsky
Project Role:	Co-PI (unpaid)
Researcher Identifier (ORCID ID):	N/A
Nearest person month worked:	0.6
Contribution to Project:	Assisted with design of ophthalmic exam and performs the fundus exam on all subjects seen at TVHCS, Nashville.

Funding Support: N/A

Name: Jennifer Lindsey
Project Role: Co-PI
Researcher Identifier (ORCID ID): N/A
Nearest person month worked: 0.36
Contribution to Project: Assisted with design of ophthalmic exam and performs the fundus exam on all subjects seen at TVHCS, Murfreesboro.
Funding Support: N/A

Name: Martin Gallagher
Project Role: Co-PI
Researcher Identifier (ORCID ID): N/A
Nearest person month worked: 0.6
Contribution to Project: Assisted with EEG troubleshooting and design of VEP protocol, trained team members on VEP analysis and quantification.
Funding Support: NIH R21 NS096483

Name: Mark Wallace
Project Role: Co-PI
Researcher Identifier (ORCID ID): N/A
Nearest person month worked: 0.6
Contribution to Project: Designed sensory integration tasks, assisted with EEG trouble-shooting, trained team members on performing EEGs, and collecting and analyzing the resulting data.
Funding Support: NIH R21 MH109225; NIH U54 HD083211

Name: Linda Hood
Project Role: Co-PI (unpaid)
Researcher Identifier (ORCID ID): N/A
Nearest person month worked: 0.36
Contribution to Project: Assisted with design of audiological exam, identified her own team members who assist with performance and analysis of audiological exam.
Funding Support:

Name: Rene Gifford
Project Role: Co-PI (unpaid)
Researcher Identifier (ORCID ID): N/A
Nearest person month worked: 0.36
Contribution to Project: Assisted with design of audiological exam, identified her own team members who assist with performance and analysis of audiological exam.
Funding Support: NIH R01 DC009404; R01 DC013117

Name: Bennett Landman
Project Role: Co-PI
Researcher Identifier (ORCID ID): N/A
Nearest person month worked: 0.36
Contribution to Project: Assisted with design of MRI exam, training members of his laboratory to perform data analysis and quantification. Helped trouble-shoot MRI at both sites.
Funding Support: NIH R01 EB017230

Name: Adam Anderson
Project Role: Co-PI
Researcher Identifier (ORCID ID): N/A
Nearest person month worked: 0.36
Contribution to Project: Assisted with design and analysis of MRI exam, set-up the MRI protocol at Fort Campbell, and helped trouble-shoot MRI at both sites.
Funding Support: NIH R21 EB024311

Name: Bret Logan
Project Role: Co-PI
Researcher Identifier (ORCID ID): N/A
Nearest person month worked: 0.36
Contribution to Project: Provides access to the Fort Campbell Intrepid Center patients and Blanchfield Hospital Radiology Department for the MRI. Assisted with navigating IRB/HRPO.
Funding Support: N/A

Name: Marc Zola
Project Role: Co-PI
Researcher Identifier (ORCID ID): N/A
Nearest person month worked: 0.36
Contribution to Project: Provides access to the Fort Campbell Intrepid Center patients, assisted with navigating IRB/HRPO, performs the EEGs, and analyzes the resting-state EEGs.
Funding Support: N/A

Name: Kara Bean
Project Role: Co-PI
Researcher Identifier (ORCID ID): N/A
Nearest person month worked: 0.36
Contribution to Project: Assisted with design of audiological exam, and performs the audiological exam at Fort Campbell.
Funding Support: N/A

Name: Angelletta Payne
Project Role: Co-PI
Researcher Identifier (ORCID ID): N/A
Nearest person month worked: 0.36
Contribution to Project: Assisted with design of ophthalmic exam and performs the fundus exam on subjects seen at Fort Campbell.
Funding Support: N/A

Name: Lucas Groves
Project Role: Co-PI
Researcher Identifier (ORCID ID): N/A
Nearest person month worked: 0.36
Contribution to Project: Assisted with design of ophthalmic exam, helped obtain approval for study at Fort Campbell, and performs the fundus exam on subjects seen at Fort Campbell.
Funding Support: N/A

Name: Cindy Chen

Project Role:	Co-PI
Researcher Identifier (ORCID ID):	N/A
Nearest person month worked:	0.6
Contribution to Project:	Assisted with design of the study and is in regular communication with the team, assuring proper study design and implementation from a statistical perspective.
Funding Support:	N/A

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

The PI was awarded two NEI grants as of September 30, 2018 (see below). She has decreased her percent effort on a collaborators' grant and her other DoD grant. No changes will be made to this grant.

R01EY022349 NEI
Role: PI; 40% effort Total Costs: $1.875M 2018-2022
Erythropoietin-mediated antioxidant pathways in glaucoma
The major goals of this project are to: 1) determine the role of the Nrf2 pathway and the antioxidant response element in EPO-R76E mediated protection of the retinal ganglion cells; and 2) quantify safety and neuroprotection in both a mouse and a non-human primate model of glaucoma using EPO-R76E loaded microparticles.

U24EY029893 NEI 2018-2023
Role: PI; 20% effort Total Costs: $8M
Retinal ganglion cell replacement in clinically relevant models of optic neuropathy
The goals of this project are to: 1) Establish a tree shrew model of glaucoma; 2) Establish a tree shrew model of blast-induced traumatic optic neuropathy; and 3) Optimize retinal ganglion cell transplantation in both models.

What other organizations were involved as partners?
No changes – collaborating with TVHCS and Fort Campbell.

8. SPECIAL REPORTING REQUIREMENTS:
None.

9. APPENDICES:
See attached updated Quad Chart.

Quantitative evaluation of visual and auditory dysfunction and multi-sensory integration in complex TBI patients

PI: Tonia S. Rex **Org:** Vanderbilt University Medical Center **Award Amount:** $2 million

Study/Product Aim(s)

Using a multi-site and multi-disciplinary approach, we will assess the physiological basis of sensory dysfunction in TBI patients, determine causal relationships between sensory dysfunction and mechanism of injury, and derive sensitive, objective, quantitative diagnostic metrics for TBI-induced sensory dysfunction.

•SA 1: To derive a combination of objective and quantitative metrics to diagnose visual and/or auditory dysfunction after TBI.

• SA 2: To identify and track alterations in the brain that underlies self-reported sensory deficits after TBI.

• SA 3: To identify deficits in multi-sensory integration and the cortical correlates of these deficits in complex TBI patients.

Approach

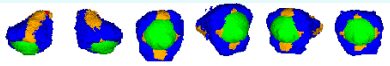
To achieve our goals while addressing the complexity of trauma we will: 1) test the efficacy of a combination of measurements used together; 2) utilize novel, sensitive assays and analysis tools to identify subtle, but functionally important damage/deficits; and 3) quantify alterations in sensory integration using psychophysiological tools within an EEG framework.

Visual System

Table 1: Visual Fields

TBI Subject	Right Eye	Left Eye
1	-1.78	-1.57
2	-4.17	-4.39
3	-0.13	-0.39

Fig. 1



Auditory System

Table 2: Middle Ear Reflex

	500 Hz	1k Hz	2k Hz	4k Hz
Ipsi	90	85	95	100 (NR)
Contra	95	95	105	100 (NR)

Table 3: Sound in Noise

Ear	Presentation Level	SNR-Loss
Right	50	6.5
Left	55	9

Table 4: Conduction Thresholds

Ear	9	10	11	12	14	16
Right	20	20	45	40	45	45
Left	15	25	35	40	45	50

Although our number of subjects is still low, we are already detecting differences between control and mTBI individuals. Visual System: Table 1. Red box indicates abnormal mean deviation in visual fields. Fig. 1. MRI segmentation of orbit and optic nerve. Auditory System: Data from TBI subjects: Table 2: Middle ear reflex in a TBI subject, Table 3: Ability to hear sound in noise, Table 4: High frequency conduction thresholds (units=kHz). Red indicates hearing loss/deficits.

Timeline and Cost

Activities CY	16	17	18	19
Specific Aim 1				
Specific Aim 2				
Specific Aim 3				
Estimated Budget ($K)	**$700**	**$650**	**$650**	

Updated: 10/02/2018

Goals/Milestones

CY17 Goal – Obtain IRB approval and recruit and screen subjects

☑ Obtain IRB approval at TVHCS and VUMC

☑ Advertise for normal controls and TBI subjects

CY18 Goal – Screen and Assess TBI and control subjects

☑ Obtain IRB approval at Fort Campbell

☑ Perform examinations, analyze results and upload data into FITBIR

☑ Meet regularly with team members

CY19 Goal – Finish assessments and compile/analyze data

☐ Perform examinations, analyze results and upload data into FITBIR.

☐ Perform data analysis and submit results for publication

Budget Expenditure to Date

Projected Expenditure: $2 million

Actual Expenditure: $215,317