AWARD NUMBER: W81XWH-17-2-0055

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

PRINCIPAL INVESTIGATOR: Tonia S. Rex, Ph.D.

CONTRACTING ORGANIZATION: Vanderbilt University Medical Center

REPORT DATE: October 2019

TYPE OF REPORT: Annual

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2019	Annual	09/15/18 – 09/14/19

4. TITLE AND SUBTITLE
Quantitative evaluation of visual and auditory dysfunction and multi-sensory integration in complex TBI patients

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-17-2-0055

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Tonia S. Rex

E-Mail: tonia.rex@vanderbilt.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

Vanderbilt University Medical Center

8. PERFORMING ORGANIZATION REPORT NUMBER

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

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

10. SPONSOR/MONITOR'S ACRONYM(S)

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

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

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. 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 to assess TBI patients from 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 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.

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

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

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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) The Vanderbilt single IRB decided to increase the risk level of the study due to the use of dilating eye drops – this was not a change in our protocol, but it was something that the committee changed their decision on during a recent review. As a result of this IRB decision change we had to set up a medical monitor and a monitoring plan and obtain DoD HRPO approval for the plan. As VUMC was reviewing our updated IRB to reflect these changes, our clinical study coordinator left, which meant that we then had to change the name on all paperwork. We finally obtained VUMC approvals months later. We only just obtained DoD HRPO approval in September.

B) Our clinical study coordinator left the position unexpectedly and with 2-weeks notice at the end of June. We hired a new study coordinator internally, she is familiar with the project and can perform EEGs and the electrophysiology aspect of the audiological assessments. However, she is not an ophthalmic technician. Therefore, we need to hire someone into that position. To solve this, we have provided percent effort to the Vanderbilt Eye Institute Clinical Trials Unit so that the ophthalmic technicians/clinical trial coordinators will perform the orthoptic assessments and technical work-up on the subjects in our study on subjects at the VEI. They received training from Ron Biernacki on orthoptic assessments. We also trained the VEI Residents on how to perform these assessments and they will do so at Fort Campbell, at least for the interim.

C) We hired an assistant for the study who we have trained to perform EEGs. This person will be responsible for the study at Fort Campbell once that site is active.

D) We purchased an EEG system for assessing subjects at Fort Campbell. The Intrepid Spirit Center has provided us space for it. We have received training and set-up support and have performed testing and optimization. The system is up and running.

E) We are continuing to advertise at VUMC and are working to gain access for our clinical study coordinator to the VA so that she can send letters to Veterans. Recruitment and advertising materials have been given to the Ophthalmology and Audiology clinics at Fort Campbell for distribution to recruit controls. Materials have also been given to Dr. Marc Zola at the Intrepid Center of Excellence at Fort Campbell for distribution to the clinic team who assesses the TBI patients.

F) We presented posters at the National Neurotrauma Symposium and the Military Health System Research Symposium. Diethelm et al. (2019) Quantitative evaluation of visual and auditory dysfunction in TBI patients: description of study and characteristics of early participants.

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.
D. To collect and analyze data.

A. Recruitment: We recruited 52 subjects and have data on just over 30 subjects (**Figure 1**). This significant shortfall is due to IRB, HRPO, and staff changes. We expect to significantly increase our numbers in the next year.

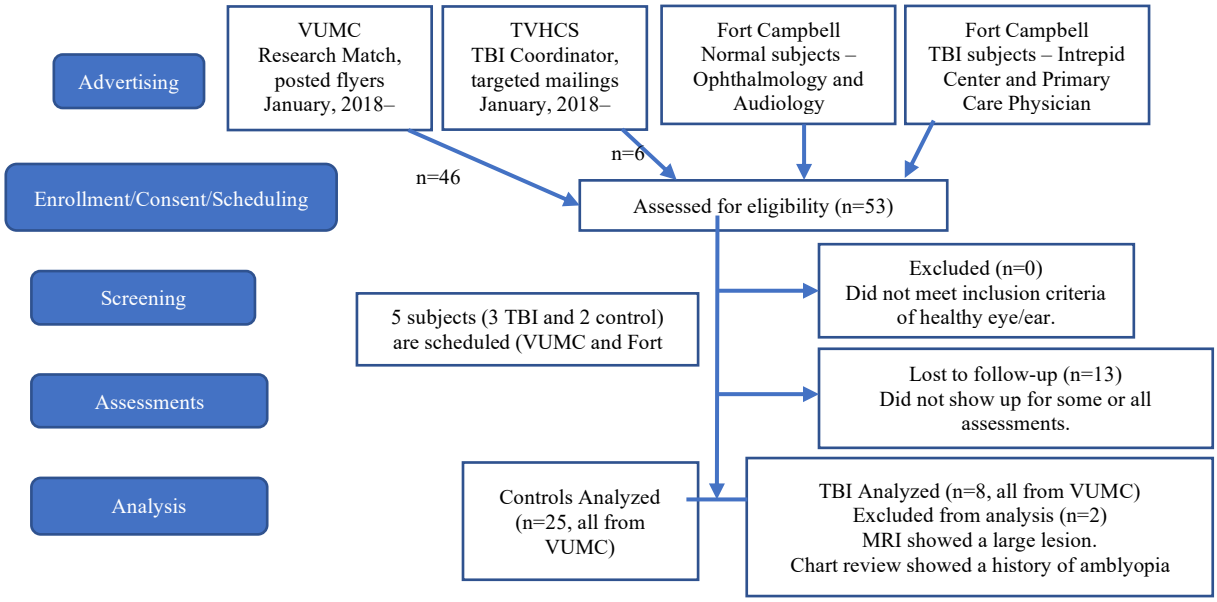


Figure 1. Flow chart of subject recruitment, enrollment, and assessments.

We have sent letters to Veterans and will do so again, once clearance is obtained for our new clinical study coordinator.

B. Regulatory approvals and recruitment at Fort Campbell: We have obtained regulatory approvals for Fort Campbell, have set-up and tested the EEG system, and have provided advertising materials to our collaborators at Blanchfield Hospital and the Intrepid Spirit Center.

C. Study demographics: Control and TBI subjects are fairly well matched in terms of age (**Figure 2**). We currently have more females in the control group (**Figure 2**).

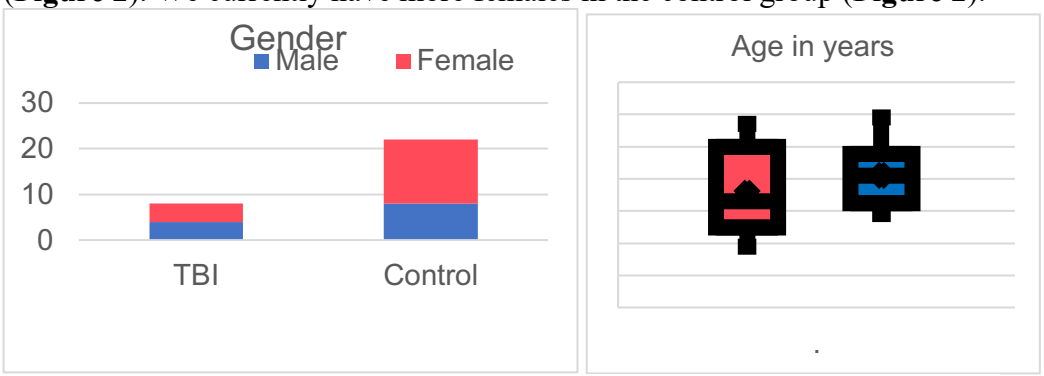


Figure 2. Quantification of gender and age in both cohorts.

D. Ophthalmology: All subjects were measured at 20/20 BCVA with refraction. We have not detected any differences in contrast sensitivity or visual fields. We have identified Accommodation deficits in most of our subjects (**Figure 3**).

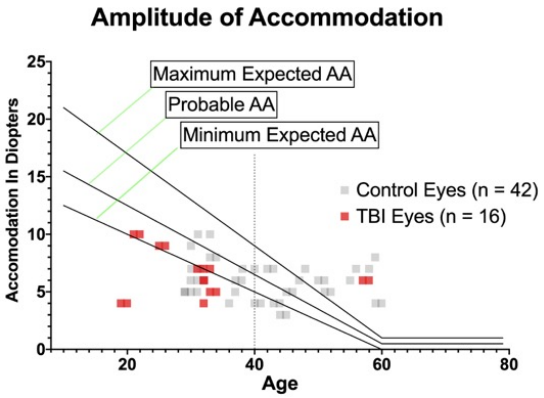


Figure 3. Graph of normative values for amplitude of accommodation. TBI subjects eyes are shown in red. Most are below the normative values as adjusted for age.

E. Audiology: All subjects to date have normal pure tone test results (**Figure 4**). However, differences in sound in noise (**Figure 4**) and some of the electrophysiological measures (data not shown) are being detected in the TBI subjects.

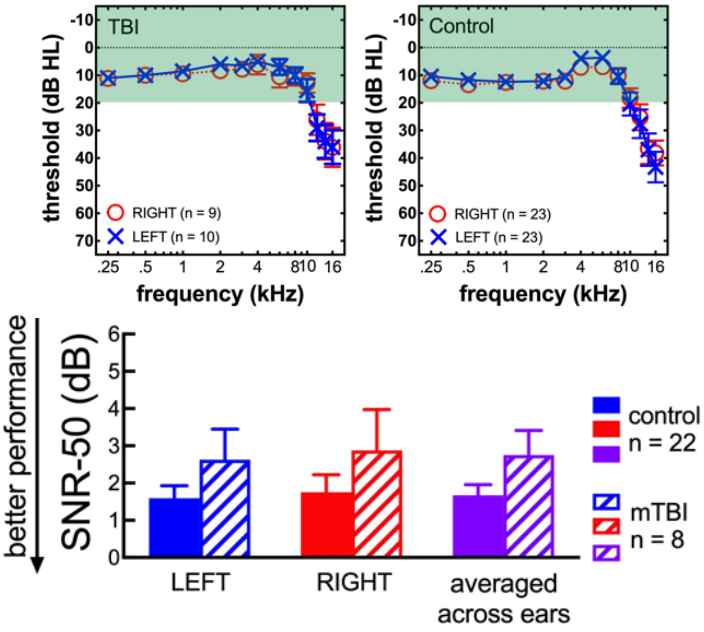
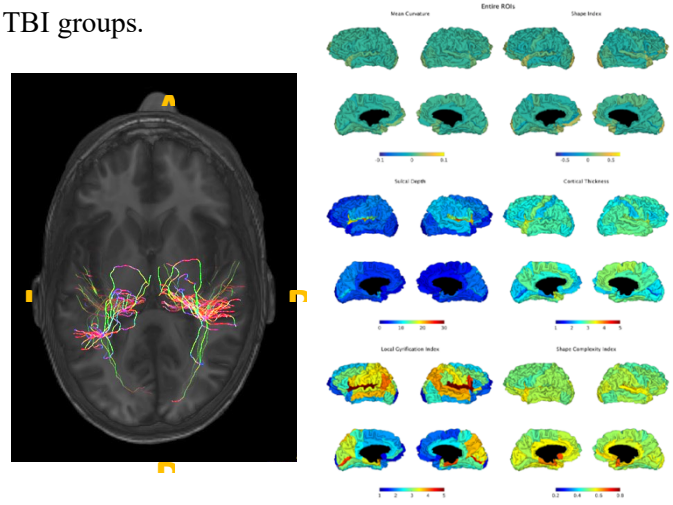


Figure 4. Top: Quantification of the pure tone test in both ears for both TBI (left) and control (right) groups. Bottom: Quantification of responses in the sound in noise test in each and both ears and in both control and TBI groups.

F. MRI: We have started to analyze the T1-weighted, diffusion-weighted, and susceptibility-weighted MRI data (Figure 5). We are using machine learning to compare controls to TBI subjects (Table 1). We have obtained 97% accuracy, 87.5% recall, and 100% specificity for mTBI subjects as compared to controls using this approach. This suggests that using machine learning on clinical MRI could potentially be used to diagnose mild TBI. We are preparing a presentation and paper on this.



Metric Set	Components	Accuracy	Recall	Specificity
DWI	11	0.830 (0.067)	0.500 (0.354)	0.958 (0.072)
T1w	13	0.964 (0.062)	0.875 (0.217)	1.000 (0.000)
Both	11	0.968 (0.054)	0.875 (0.217)	1.000 (0.000)

G. We are developing Matlab tools to analyze the resting state EEG, VEP, and sensory integration EEG data.

4. IMPACT:

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

I was invited to participate in VCE activities to use data from this study and others to encourage clinicians to measure accommodation in TBI patients in a standardized manner.

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:

The VUMC IRB decided that clinical standard of care dilating eye drops were greater than minimal risk. This required us to set up an external monitor and reporting system. We have since done so.

Actual or anticipated problems or delays and actions or plans to resolve them:

We are still awaiting access for Catherine Diethelm to the VA system so that she can mail out letters to Veterans. Dr. Chomsky has intervened to help move the process along.

Changes that had a significant impact on expenditures:

We have had to provide percent effort to the VEI CTU in order to have an ophthalmic technician performed the necessary assessments.

Significant changes in use or care of human subjects:

Nothing to report.

6. PRODUCTS:

Publications, conference papers, and presentations:

Diethelm et al. Quantitative evaluation of visual and auditory dysfunction in TBI patients: description of study and characteristics of early participants. National Neurotrauma Symposium July, 2019

Diethelm et al. Quantitative evaluation of visual and auditory dysfunction in TBI patients: description of study and characteristics of early participants. Military Health System Research Symposium. August, 2019

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?

Nothing to report.

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.

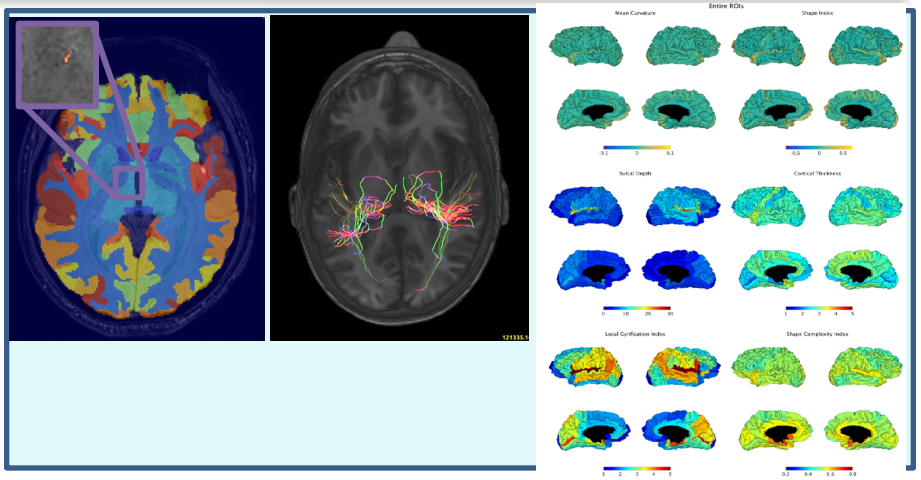
•SA 1: To derive a combination of objective and quantitative metrics to diagnose visual and/or auditory dysfunction after TBI.

• 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.



We have collected and analyzed SWI, DWI and structural information from the MRI scans in controls and TBIs. Left: A microbleed in a TBI subject. Middle: Tractography. Right: heatmaps of structural changes in curvature, shape, volume, thickness, and depth between TBI and control subjects.

Timeline and Cost

Activities CY	17	18	19	20
Specific Aim 1				
Specific Aim 2				
Specific Aim 3				
Estimated Budget ($K)	**$250**	**$500**	**$500**	**$750**

Updated: 06/29/2019

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: $716,544.25