AWARD NUMBER: W81XWH-17-2-0055

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

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CONTRACTING ORGANIZATION: Vanderbilt University, Nashville, TN

REPORT DATE: October 2021

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 2021	Annual	15Sep2020-14Sep2021

4. TITLE AND SUBTITLE

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

5a. CONTRACT NUMBER
W81XWH-17-2-0055

5b. GRANT NUMBER
PT160103

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

Vanderbuilt University, Nashville TN

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	19	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:
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:

We were invited to present a talk and a poster at MHSRS. Unfortunately, it was canceled due to COVID-19. We presented virtual posters at the National Neurotrauma Symposium.

2) Specific Objectives:

A. Recruitment: We have data on 61 subjects to date. All recruitment and assessments have occurred at VUMC. Due to COVID-19 this will continue to be the case.

B. Regulatory approvals and recruitment: We have obtained regulatory approvals and a pathway for recruitment and assessments. Unfortunately, due to COVID-19 non-VUMC sites are closed to clinical research. Therefore, we are focusing on VUMC.

C. Study demographics: We have added TBI subjects and now have similar numbers of control and TBI subjects (33 vs. 28). The age discrepancy between groups has also decreased, however, we are still incorporating an age adjustment into the data as appropriate.

D. Ophthalmology: All subjects were measured at 20/20 BCVA with refraction and had a normal fundus exam. As previously reported, we continue to detect differences in accommodation amplitude in the TBI subjects compared to controls. The OCT data shows differences ($p<0.05$) between these groups. The peripapillary retinal nerve fiber layer (RNFL) is thinner in the TBI group in the temporal region (**Fig. 1A**). However, it is thicker in the superonasal region (**Fig. 1A**). The order of presentation is flipped for the ganglion cell layer (GCL) thickness, however, red still indicates the TBI group (**Fig. 1B**). The GCL is thinner in the superior perifoveal region

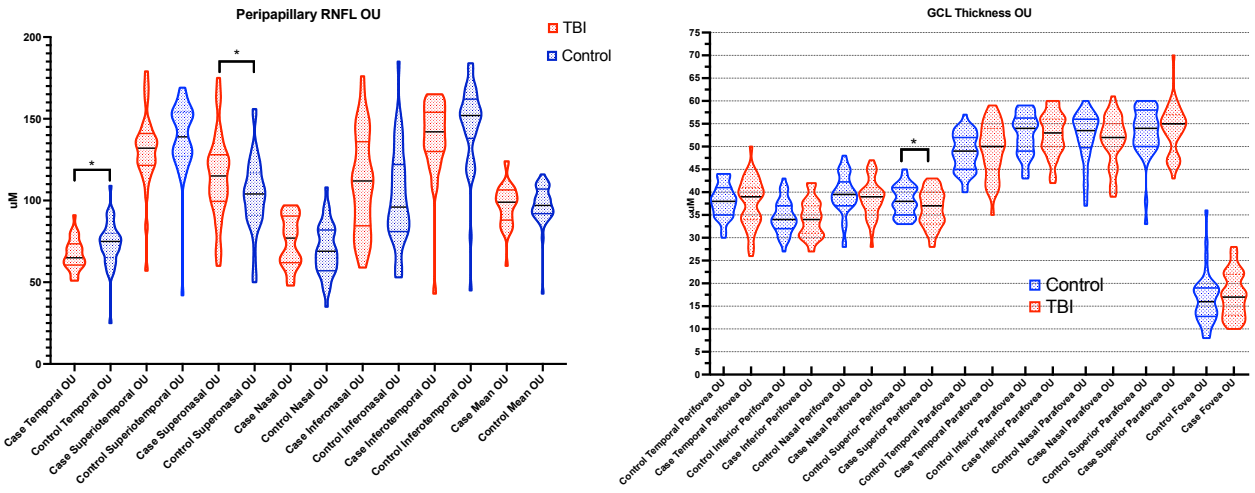


Figure 1. Quantification of OCT data: A) Peripapillary retinal nerve fiber layer (RNFL) thickness, B) Ganglion cell layer (GCL) thickness.

in the TBI group. The high individual variability is known to exist and demonstrates the strength of longitudinal OCT measurements whenever possible. However, the fact that we are detecting group differences is compelling and agrees with the few longitudinal OCT studies on TBI subjects that have been performed to date.

No group differences were detected in the Humphrey visual field (HVF) foveal sensitivity (**Fig. 2A**) or mean deviation (**Fig. 2B**) assessments. However, there were outliers in the TBI, but not the control, groups. We will follow up to see if the subjects that performed poorly on the visual fields also showed deficits in other assessments. We also have brought MAJ Lucas Groves, MD, who is now checking the quality of the OCT and VF images to assure they meet clinical threshold standards.

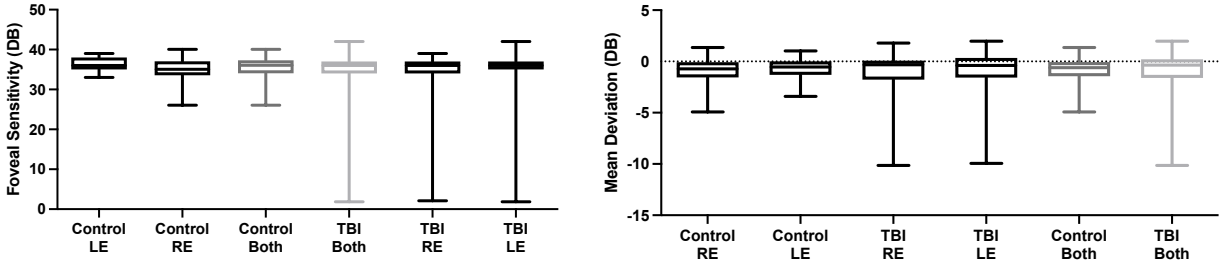


Figure 2. Quantification of foveal sensitivity (A) and mean deviation (B) by HVF in age-matched groups.

E. Audiology: All subjects to date have normal pure tone test and sound in quiet results. While we are still recruiting, scheduling, and assessing subjects, we have also started to analyze the data. Data from 59 subjects were available at the time of these analyses. Four participants were excluded from analyses because they did not have ABR data. Six participants were excluded from analyses because they did not have LLR data. Four additional participants were excluded from analyses because they did not meet criteria for near-normal hearing defined as thresholds of 30 dB HL or better for all frequencies for both ears. One other participant was excluded from analyses because they were assigned an "excluded" study arm due to non-audiological reasons. Thus, data from 50 subjects were included in the ABR analyses and 47 were included in the LLR analyses.

We began by assessing for differences between right and left ears for all dependent variables using paired t-tests corrected for multiple comparisons using the Bonferroni criteria. These analyses were conducted in order to determine if further analyses needed to be conducted on each ear separately. The auditory brain response (ABR) Wave V peak-to-peak amplitude was significantly larger in the right ear compared to the left ear in the ipsilateral channel and Wave III peak-to-peak amplitude was significantly larger in the left ear compared to the right ear in the contralateral channel. There is no ready explanation for these subtle ear differences. Based on these findings, further analyses were completed on each ear separately. For consistency, the LLR was also analyzed from each ear separately even though no differences were identified.

The ABR absolute latency, inter-wave latency, and peak-to-peak amplitude followed established trends for the ipsilateral and contralateral recordings for both ears. This provides a validation of the quality of our ABR data. Similarly, we assessed for differences among long latency response (LLR) waveform components using paired t-tests corrected for multiple comparisons. These analyses were completed in order to assess for established LLR trends to validate our data. LLR absolute latency and peak-to-peak amplitude followed established trends for the ipsilateral and contralateral recordings for both ears. This provides a validation of the quality of our LLR data.

We generated linear models for each dependent variable for each ear separately with predictor variables of group (case vs. control), sex (female vs. male), and age (continuous variable) as well as interactions among predictor variables.

ABR absolute latency: ABR absolute latency does not differ between individuals with mTBI and controls for any waveform component for either ear. The effect of sex is significant for ipsilateral Wave V latency in the right ear (p=0.0415) and approaches significance in the left ear (p=0.0906). Participant age is positively correlated with ipsilateral Wave I latency in the right ear (p=0.0699) and the left ear (p=0.022) and with ipsilateral Wave V latency in the right ear (p=0.0683) and the left ear (p=0.0895). These effects are consistent with males having longer ABR Wave V latencies compared to females and for older age to partially contribute to longer Wave I and Wave V latencies. There are no notable effects for the contralateral channel recordings for either ear. These findings are consistent with sex and age findings previously reported in other studies.

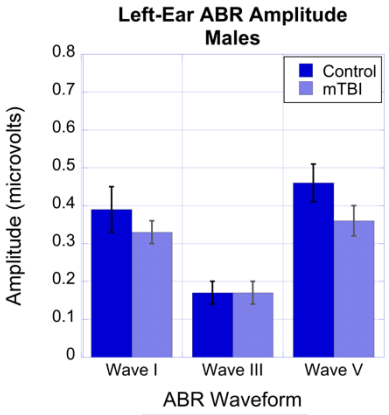


Figure 3.

ABR peak-to-peak amplitude: We did not observe statistically significant differences in ABR peak-to-peak amplitude measures compared between individuals with mTBI and typical controls. However, a trend was observed wherein males with mTBI appear to have lower ABR peak-to-peak amplitudes compared to male controls (**Fig. 3**). This trend was not observed for females with mTBI. Participant age is negatively correlated with ipsilateral Wave I amplitude in the left ear (p=0.0174) and with Wave III amplitude in the right ear (p=0.00756) and the left ear (p=0.0353). This is consistent with older age partially contributing to lower Wave I and III amplitudes. The effect of sex is significant for Wave III amplitude in the left ear only (p=0.0395). The interaction between sex and age for Wave III amplitude in the left ear approaches significance (p=0.0810). These findings are consistent with males, especially older males, having smaller Wave III amplitudes in the left ear compared to females. There are no notable effects for the contralateral channel recordings. Our sex and age findings are consistent with findings previously reported in other studies. **The potential trend of lower ABR amplitudes for males with mTBIs should be monitored for significance as group membership increases.**

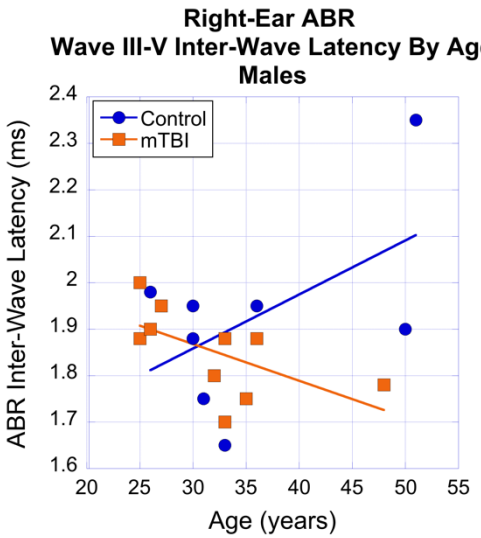


Figure 4.

ABR inter-wave latency: The interaction between group, age, and sex is significant for the ipsilateral III-V inter-wave latency in the right ear only (p=0.0335). The interaction between group and sex approaches significance (p=0.0784) for the ipsilateral III-V inter-wave latency in the right ear only (**Fig. 4**). **These interactions suggest that older males with mTBI have a shorter ipsilateral III-V inter-wave latency in their right ears. Physiologically speaking, this**

would suggest that older males with mTBI have a shorter conduction time along the rostral auditory brainstem neural pathway. There are no notable effects for the contralateral channel recordings. These findings should be considered with caution since the effect is only observed in the right ear and may be partially driven by an outlier data point in the control group.

LLR absolute latency: The effect of group approached statistical significance for P2 absolute latency in the right ipsilateral (p=0.0954) and contralateral (p=0.0517) channels. The interaction between group and age approached statistical significance for P2 absolute latency in the right ipsilateral (p=0.0524) and right contralateral (p=0.0654) channels. These effects are consistent with individuals with mTBI potentially having shorter P2 absolute latencies compared to controls. There are no notable effects for the left ear recordings for either channel.

LLR peak-to-peak amplitudes:

P1-N1 peak-to-peak amplitude: The effects of group and age as well as the interaction between group and age for P1-N1 peak-to-peak amplitude were statistically significant in the right and left ipsilateral channels (**Fig. 5**) and left contralateral channel. Additionally, the effect of sex and interaction between age and sex were statistically significant in the left ipsilateral channel and approached statistical significance in the left contralateral channel. The effect of age and interaction between group and age were statistically significant for P1-N1 peak-to-peak amplitude in the right contralateral channel (**Fig. 6**). **Together, these results are consistent with older females with mTBI having reduced P1-N1 peak-to-peak amplitudes.**

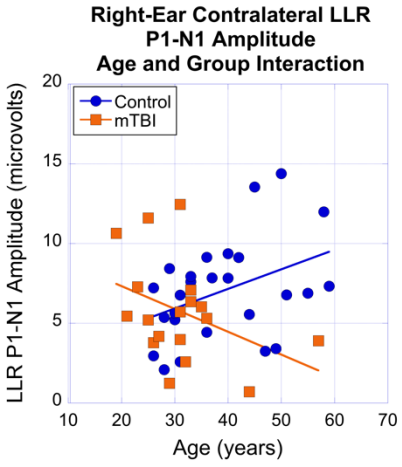


Figure 5.

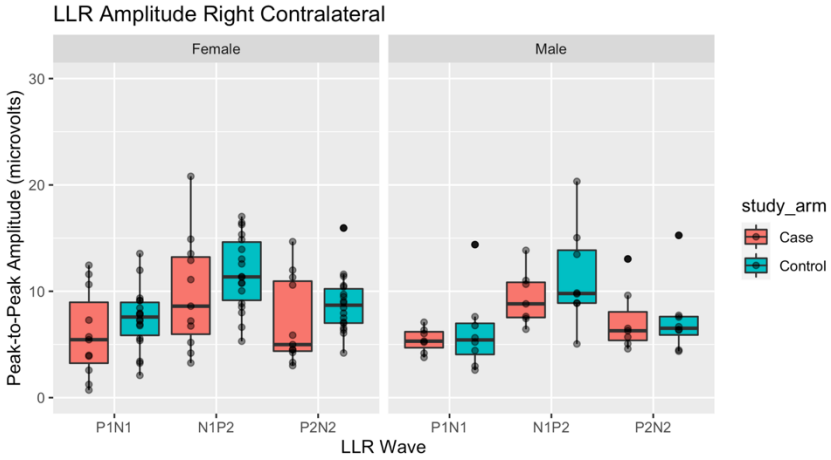


Figure 6.

N1-P2 peak-to-peak amplitude: The effect of sex and interaction between age and sex for N1-P2 peak-to-peak amplitude were statistically significant in the left ipsilateral channel only (**Fig. 7**) and approached statistical significance in the right contralateral channel. The effect of age and interaction between group and age for N1-P2 peak-to-peak amplitude approached statistical significance in the right ipsilateral channel. The effects of age and sex approached statistical significance in the left contralateral channel. **Together, these results may suggest that older females with mTBI have reduced N1-P2 peak-to-peak amplitudes.**

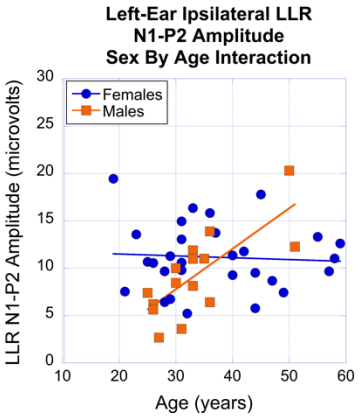


Figure 7.

P2-N2 peak-to-peak amplitude: The effect of age was statistically significant for P2-N2 peak-to-peak amplitude in the right ipsilateral channel and approached statistical significance in the right contralateral channel. Additionally, the effect of sex and interaction between age and sex for P2-N2 peak-to-peak amplitude were statistically significant in the left ipsilateral channel (**Fig. 8**). The three-way interaction between group, age, and sex for P2-N2 peak-to-peak amplitude approached statistical significance in the left ipsilateral channel. **Together, these results may suggest that older females with mTBI have reduced P2-N2 peak-to-peak amplitudes.**

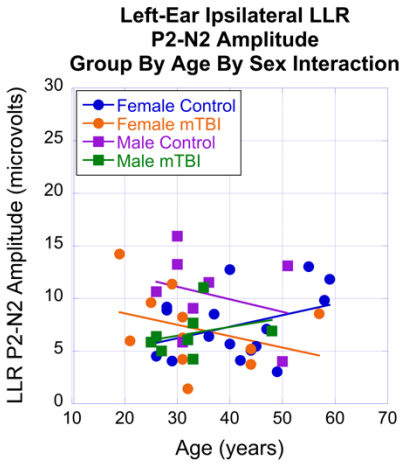


Figure 8.

G. MRI: We have identified brain regions that differ in their size/shape from controls by a z-score of 3 or higher. **Fig. 9** shows a representative z-score heat map of a TBI subject brain. **Fig. 10** shows the number of control and TBI subjects with a z score of greater than 3 in terms of the difference in size from the control average. While a lot of variability is present in the left subcallosal area, most of the areas have very few normals in this range outside of normal average values. Multiple areas differed signifi

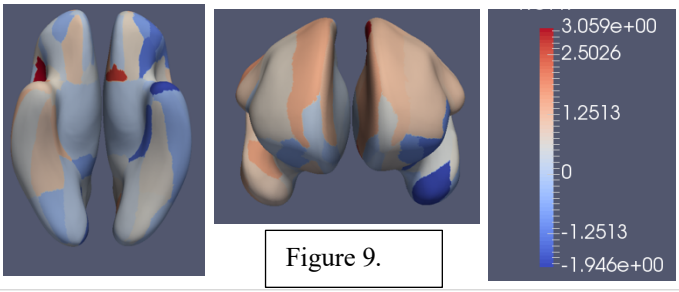


Figure 9.

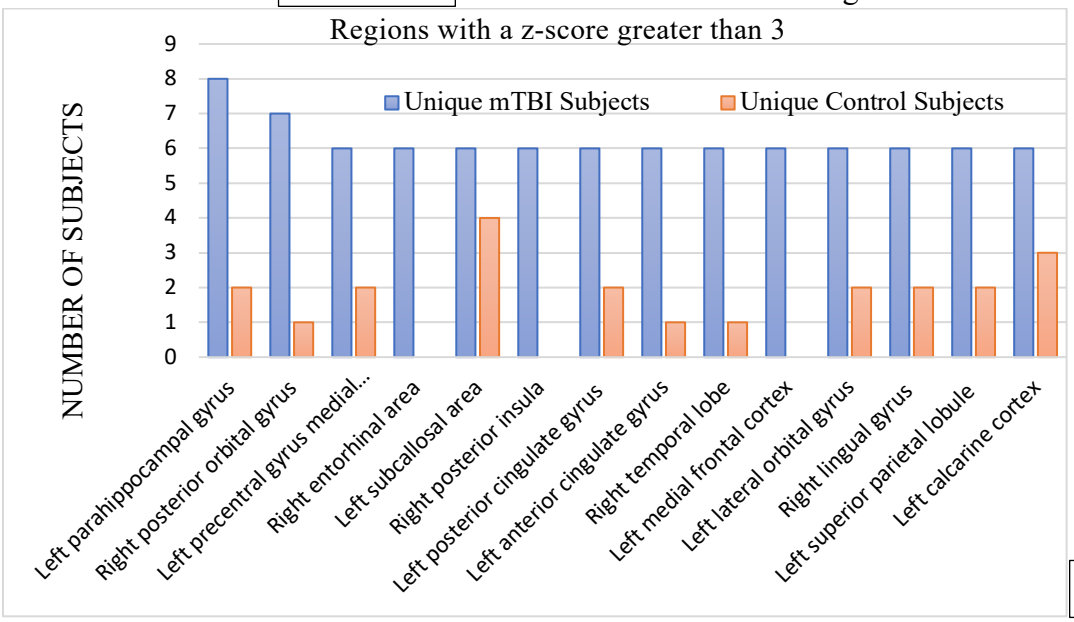


Figure 10.

cantly in size in TBI subjects only including the right entorhinal area, right posterior insula, and left medial frontal cortex. Several other areas were different in many TBI subjects but only 1-2 control subjects: left parahippocampul gyrus, right posterior orbital gyrus, left precentral gyrus medial segment, left posterior and left anterior cingulate gyri, right temporal lobe, left lateral orbital gyrus, right lingual gyrus, and left superior parietal lobe. Descriptions of the functions of each of these brain regions are listed in **Table 1**. Not surprisingly, several areas are associated with cognition, memory, and emotion – all functions known to be altered by TBI. Particularly interesting for our study is the detection of size differences in three visual areas: the right lingual gyrus, left superior parietal lobe, and the left calcarine cortex (i.e. visual cortex). We then looked for correlations between these three visual areas and self-reported visual symptoms from the NBSI as shown in **Table 2.**

Table 1.

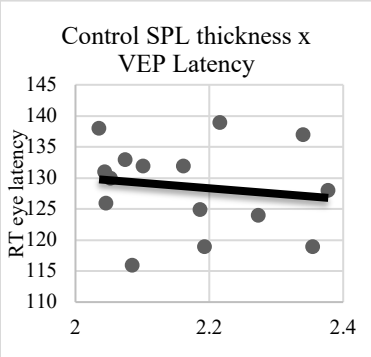
Region	Function
Left Parahippocampal Gyrus	Spatial memory and navigation
Right Posterior Orbital Gyrus	Odor perception
Left Precentral Gyrus Medial Segment	Voluntary motor movement
Right Entorhinal Area	Higher-order processing and memory
Left Subcallosal Area	Emotion and fear response
Right Posterior Insula	Thermosensory function and pain perception
Left Posterior Cingulate Gyrus	Cognition
Left Anterior Cingulate Gyrus	Emotion and decision making [21]
Right Temporal Lobe	Sensory processing, language, memory [22] – [23]
Left Medial Frontal Cortex	Attention, organizing motor response, evaluating risk [24]-[26]
Left Lateral Orbital Gyrus	Odor perception [15]
Right Lingual Gyrus	Visual processing, specifically familiar scenes and faces [27]
Left Superior Parietal Lobe	Visuospatial perception and attention [28]
Left Calcarine Cortex	Visual processing, specifically color processing and orientation [28]

Surprisingly there was no clear correlation between self-reported systems and the size differences detected by MRI for the TBI subjects reporting mild to moderate symptoms. In contrast, the two subjects who reported very severe vision problems and severe light sensitivity also had significant size differences in all three visual areas. Next, we looked for correlations between the size differences in the visual areas and deficits that we have detected in the VEP (presented in our last report). No correlations were detected in the control subjects. In contrast, we detected a statistically significant correlation between superior parietal lobe thickness and the VEP latency in the TBI subjects, R= 0.879, p= 0.002 (**Fig. 11**).

Table 2

	TBI… [VKY]	TBI… [EPV]	TBI… [DE0]	TBI… [PV9]	TBI… [ZXA]	TBI… [DF3]	TBI… [GKQ]	TBI… [HZW]	TBI… [BZP]	TBI… [YX6]	TBI… [VK3]	TBI… [VVV]	TBI… [HJG]	
NBSI Self-Reported Vision Problems	Mild	Mild	None	Moderate	Moderate	None	Very Severe	None	None	None	None	Very Severe	Mild	Mild

NBSI Self-Reported Light Sensitivity	Moderate	Severe	None	Mild	Moderate	None	Severe	None	None	None	Mild	Severe	Moderate	Severe
Right Lingual Gyrus z-score greater than 3	No	No	No	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	No
Left Superior Parietal Lobe z-score greater than 3	No	No	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	No	No
Left Calcarine Cortex z-score greater than 3	Yes	Yes	No	No	Yes	No	No	Yes	Yes	No	No	No	No	Yes



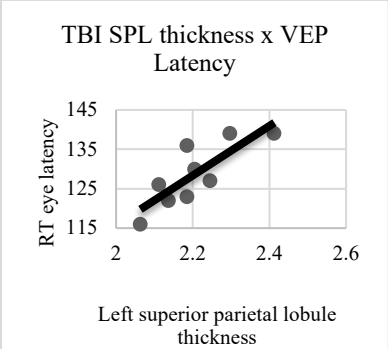


Figure 11.

H. We are using our Matlab tools to analyze the resting state EEG, VEP, and sensory integration EEG data. We are continuing to analyze MRI findings and to make correlations across assessments. At the same time we are actively recruiting and have about 10 additional individuals we are currently scheduling for assessments.

4. IMPACT:

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

We have contributed to change in practice for TBI patients seen in optometry or ophthalmology clinics in the DoD. Using our MRI dataset we have demonstrated the potential power of machine learning to pull out differences between TBI and control subjects.

What was the impact on other disciplines?

We have published two papers in SPIE. We have presented multiple posters and talks at three different conferences.

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:

Both Fort Campbell and TVHSC are still closed to non-COVID-19 related clinical research. The study is being performed exclusively at VUMC.

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

Our clinical study coordinator took a job elsewhere. We were able to fill his role with multiple other personnel with only a brief gap in between.

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 perform the necessary assessments. We are also providing effort to audiologists to perform those assessments. However, to save money for adding participants during this NCE, we have decreased percent effort for faculty.

Significant changes in use or care of human subjects:

Nothing to report.

6. PRODUCTS:

Publications:

Kerley CI, Schilling KG, Blaber J, Miller B, Newton A, Anderson AW, Landman BA, **Rex TS**. (2020) MRI correlates of chronic symptoms in mild traumatic brain injury. *SPIE Medical Imaging*, International Society for Optics and Photonics, 2020.

Schilling KG, Blaber J, Hansen C, Rogers B, Anderson AW, Smith S, **Rex TS**, Kanakaraj P, Resnick SM, Cutting L, Woodward N, Zald D, Landman BA. (2020) Distortion correction of diffusion weighted MRI without reverse phase-encoding scans or field-maps. *PLoS One* 15:e0236418

Elenberger J, Kim B, de Castro-Abeger A, **Rex TS.** (2020) Potential role for intrinsically photosensitive retinal ganglion cell dysfunction in TBI symptomology. *Neurology* Epub.

Kerley CI, Cai L, Yu C, Crawford LM, Schilling KG, Landman BA, **Rex TS.** (2021) Joint analysis of structural connectivity and cortical surface features: correlates with mild traumatic brain injury. *SPIE Medical Imaging*. Epub

Conference papers and presentations:

Kerley C, Schilling KG, Blaber J, Miller B, Newton A, Anderson AW, Landman BA, **Rex TS.** (2020) MRI correlates of chronic symptoms in mild traumatic brain injury. SPIE IP:MI. Houston, TX

Elenberger J, Crawford L, Singh E, Kerley C, Chen Q, Lavin P, Landman B, Anderson A, Colyer M, **Rex TS.** (2020) Ophthalmological findings from a pilot study of chronic mTBI subjects. Southeastern Vision Conference

Elenberger J, Crawford L, Singh E, Diethelm C, Lavin P, Kerley C, Anderson A, Landman B, **Rex TS**. (2020) Preliminary visual findings in mild TBI patients. Southeastern Vision Research Conference. poster.

Kerley CI, Cai L, Yu C, Crawford LM, Elenberger JM, Singh ES, Schilling KG, Aboud K, Landman BA, **Rex TS.** (2021) Joint analysis of structural connectivity and cortical surface features: correlates with mild traumatic brain injury. *SPIE Medical Imaging*: *Image Processing*. San Diego, CA. Oral Presentation

Singh E, Kerley CI, Crawford L, Elenberger J, Longmuir R, Anderson A, Landman B, **Rex TS**. (2021) Structural changes in visual areas detected by MRI in chronic mild TBI subjects. *Military Health Services Research Symposium* Cancelled due to COVID-19. Oral Presentation

Al Hussein Al Awamlh S, Crawford L, Elenberger J, Singh E, Diethelm C, Chen Q, Lavin P, Longmuir R, **Rex TS**. (2021) Few ophthalmological deficits in mild TBI subjects compared to age-matched controls. *Military Health Services Research Symposium* Cancelled due to COVID-19

Singh E, Kerley CI, Crawford L, Elenberger J, Longmuir R, Anderson A, Landman B, **Rex TS**. (2021) Structural changes in visual areas detected by MRI in chronic mild TBI subjects. *National Neurotrauma Symposium* virtual due to COVID-19

Al Hussein Al Awamlh S, Crawford L, Elenberger J, Singh E, Diethelm C, Chen Q, Lavin P, Longmuir R, **Rex TS**. (2021) Few ophthalmological deficits in mild TBI subjects compared to age-matched controls. *National Neurotrauma Symposium* virtual due to COVID-19

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

Name:	Reid Longmuir
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 VUMC. Note: Dr. Lavin retired this summer. So, Dr. Longmuir has taken over this role.
Funding Support:	N/A

Name:	Martin Gallagher
Project Role:	Co-PI (unpaid)
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 (unpaid)
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 (unpaid)
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 (unpaid)
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:	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, performing quality assurance of OCT and VF exams.
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 study design and assures 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?

All PIs (except for Dr. Rex) have agreed to be unpaid during this NCE in order to direct funds to individuals performing exams and analyses and to support the cost of the exams and incentives to the subjects. TVHCS and Fort Campbell personnel are removed.

What other organizations were involved as partners?

No longer able to collaborate with TVHCS and Fort Campbell due to COVID-19 restrictions.

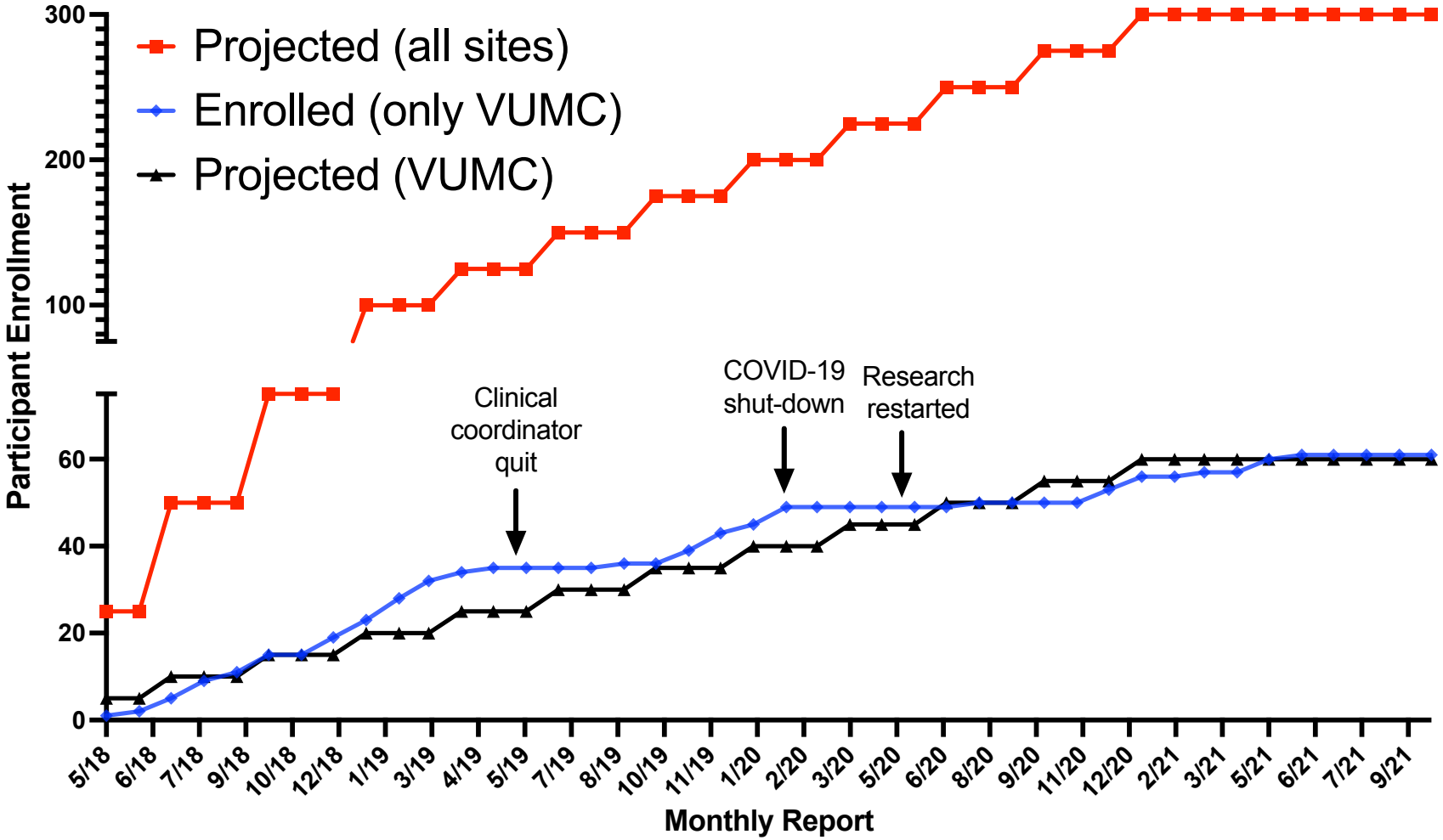
8. SPECIAL REPORTING REQUIREMENTS:

None.

9. APPENDICES:

See attached updated Quad Chart and enrollment data.

Recruitment and Retention

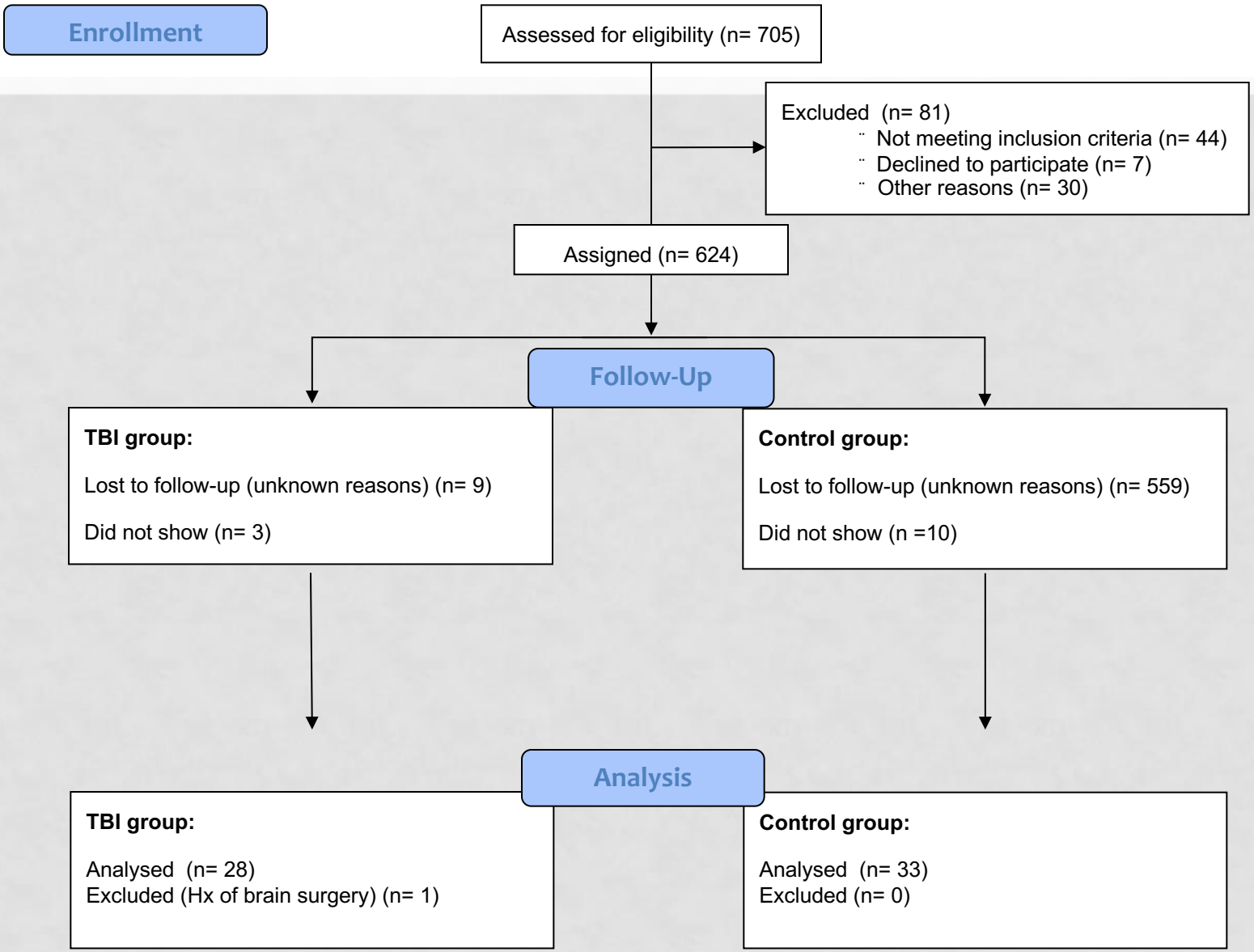


Percent of participants that complete study	**9.8%**

- TVHCS and Ft. Campbell assessed 0 subjects for reasons explained within previous DoD reports.
- We had predicted to assess **60** subjects at VUMC over the timespan of the grant period (Table).
- Despite two shut-downs of the project – due to the need to suddenly replace the study coordinator and due to COVID - we have assessed **61** subjects at VUMC.
- Therefore, we have exceeded our goal for this site.
- We have **10** additional individuals who have expressed interest and we are currently scheduling.

	Year 1				Year 2			
Target Enrollment	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
VU/VUMC			10	10	5	5	5	5
Ft. Campbell			30	30	15	15	15	15
TVHCS			10	10	5	5	5	5
Target Enrollment	0	0	50	50	25	25	25	25
	Year 3				Year 4			
Target Enrollment	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
VU/VUMC	5	5	5	5	N/A	N/A	N/A	N/A
Ft. Campbell	15	15	15	15	N/A	N/A	N/A	N/A
TVHCS	5	5	5	5	N/A	N/A	N/A	N/A
Target Enrollment	25	25	25	25				

CONSORT Diagram



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.

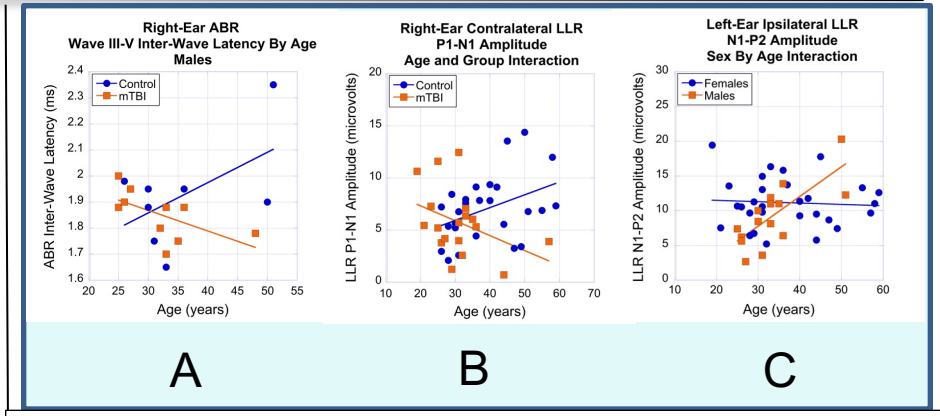
•SA 1: To derive a combination of objective and quantitative metrics to diagnose visual and/or auditory dysfunction after TBI.

• 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.



Correlation graphs of audiological data in controls and mTBI participants over age and/or sex. (A) shows that older males with mTBI have a shorter conduction time along the rostral auditory brainstem neural pathway. (B,C) shows that older females with mTBI have reduced P1-N1 peak-to-peak amplitudes (B) and N1-P2 peak amplitudes (C).

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: 10/20/2021

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 – Continue assessments and compile/analyze data
☑ Perform examinations, analyze results and upload data into FITBIR.
☑ Perform data analysis and submit results for publication

CY20 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: $1,695,192