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TITLE: TBI Exosomal Activity in Military Personnel: Perivascular Space and Role of Indicators of Sleep Metrics TEAM PRISM

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CONTRACTING ORGANIZATION: Johns Hopkins University, Baltimore, MD

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14. ABSTRACT

Objective: Determine if proteins in the blood are related to chronic neurological symptoms, poor sleep, and possibly neuro-imaging differences after a traumatic brain injury (TBI).

Study Design: We will use already collected clinical data, polysomnograms (PSG) sleep studies, imaging data, neuropsychological tests, and blood samples from service members with at least one TBI (n=300) and without any TBI (n=50) from an ongoing study at the National Intrepid Center of Excellence (NICoE) in SMs. We will use our developed methods to isolate brain-specific exosomes and examine their contents. We will also measure circulating blood concentrations of neuronal, brain barrier function, inflammation, and clearance-related proteins.

15. SUBJECT TERMS
None listed.

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1. **Introduction:** Objective: Determine if proteins in the blood are related to chronic neurological symptoms, poor sleep, and possibly neuro-imaging differences after a traumatic brain injury (TBI). Study Design: We will use already collected clinical data, polysomnograms (PSG) sleep studies, imaging data, neuropsychological tests, and blood samples from service members with at least one TBI (n=300) and without any TBI (n=50) from an ongoing study at the National Intrepid Center of Excellence (NICoE) in SMs. We will use our developed methods to isolate brain-specific exosomes and examine their contents. We will also measure circulating blood concentrations of neuronal, brain barrier function, inflammation, and clearance-related proteins.
2. **Keywords:** Traumatic brain injury, concussion, sleep, magnetic resonance imaging, perivascular spaces, glymphatics.
3. **Accomplishments:**

Major goals for this period:

Specific Aim 1: Compare levels and ratios of neural, brain barrier function, inflammation, and clearance-related proteins in blood- and brain-derived exosomes in SMs with TBIs (n=200) to controls (SMs without TBIs, n=100).

Major tasks for this period (Aim 1): Complete needed regulatory documents to obtain blood samples, MRIs, PSGs, psychological test results, and demographic data.

Accomplishments for this period

Subtask 1: OHSU approved an exempt protocol to obtain de-identified data, neuroimaging files and sleep studies.

Subtask 2: Develop a material transfer request between Johns Hopkins University, Walter Reed National Military Medical Center, and OHSU to transfer samples and data. A three-way CRADA was submitted to Walter Reed and is currently being processed with an estimated approval date of 12/01/23.

Specific Aim 2: In SM with TBIs, determine the relationship between slow-wave sleep and PVS burden, and the relationship between PVS burden and brain-derived exosomal proteins.

Major tasks for this period (Aim 2): Transfer of polysomnograms, MRI, psychological test results, and demographic data (n=300 subjects) from WRNMMC to OHSU.

Subtask 1: Develop a pipeline for MRI analysis. Investigators at WRNMC have identified a dummy/phantom file to be transferred to OHSU in November of 2023, to ensure compatibility with the perivascular detection algorithm. Dr. Piantino (PI) has received FITBIR General User Identifiers (GUIDS) from 130 NICoE members. After optimizing our perivascular space detection algorithm to this particular cohort, we will start the analysis of these datasets.

Opportunities for training and professional development: Dr. Piantino is an early-stage investigator with expertise in TBI and advanced neuroimaging techniques used to quantify glymphatic function. Over the past year, Drs. Piantino and Gill met regularly to discuss the project's progress. In addition, virtual meetings were held with the rest of the team to discuss analysis if sleep data. Dr. Piantino also participated at the 2023 Military Health System Research Symposium (MHSRS) and was an invited speaker at the "Glymphatics/sleep/cognition" session, where he presented data on perivascular spaces in veterans with blast-related mTBI.

How were the results disseminated? Dr. Piantino presented at the 2023 MHSRS meeting in Orlando, Fla.

What do you plan to do during the next reporting period to accomplish the goals? Once the three-way CRADA is approved, we will have access to the entire NOCoE sleep and MRI dataset. In the meantime, we plan to analyze MRIs available via FITBIR.

4. Impact

Our knowledge of the effects of TBI and post-traumatic sleep disruption on biological processes such as glymphatic function can be extrapolated to other high-risk populations such as young adults participating in college sports. To this effect, Dr. Piantino has obtained NIH funding (R21) to study the effects of sports-related concussion and poor sleep on a large cohort of healthy young adults.

5. Changes/Problems

Our CRADA was delayed due to short staffing at WRNMC. Other than this delay, we have not had significant deviations to our initially proposed goals.

6. Products

Presentations: Dr. Piantino has presented data on perivascular spaces and sleep at the 2023 MHSRS meeting.

7. **Participants & Other Collaborating Organizations**

   Name: Laura Dennis

   Project Role: Imaging analyst

   Nearest person month worked: 1

   Contribution to the project: Ms. Dennis has optimized the MRI-visible perivascular space detection algorithm, and adapted it to cohorts of young adults.

8. **Special Reporting Requirements: N/A**

9. **Appendices: N/A**