AWARD NUMBER: W81XWH-22-2-0079

TITLE: Elucidating the Role of Increased Neuroinflammation and Related Structural and Functional Neurological Sequelae After Exposure to Repetitive Blast

PRINCIPAL INVESTIGATOR: Stephen Ahlers, Ph.D.

CONTRACTING ORGANIZATION: The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, MD

REPORT DATE: October 2023

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development 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 2023	Annual	30Sep2022 – 29Sep2023

4. TITLE AND SUBTITLE

Elucidating the Role of Increased Neuroinflammation and Related Structural and Functional Neurological Sequelae After Exposure to Repetitive Blast

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-22-2-0079

5c. PROGRAM ELEMENT NUMBER

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

6. AUTHOR(S)

Stephen Ahlers, Ph.D.

Courriel : stephen.t.ahlers.civ@health.mil

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

The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc.
6720-a Rockledge Dr. Ste 100
Bethesda, MD 20817-1891

Naval Medical Research Center

8. PERFORMING ORGANIZATION REPORT NUMBER

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

U.S. Army Medical Research and Development 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 (appr 200 words) The effort will examine the role of brain inflammation in response to chronic, repetitive blast exposure in active-duty military populations, veterans, and in an established animal model. The program will use multiple blood-based tests as well as brain imaging, which may be used in the future for detection and treatment of neurological injury in individuals with repetitive blast exposure. The program consists of four distinct projects examining the role of neuroinflammation in the manifestation of physiological and neurological sequalae resulting from repetitive low-intensity blast overpressure exposure.

Project 1: Exploring neuroinflammation in blast-exposed operational personnel.
Project 2: Neuroinflammation in Active-Duty SM with Diagnosed TBI.
Project 3: Neuroinflammation in Veterans with Diagnosed, Chronic TBI.
Project 4: Understanding the interplay between neuroinflammation and cerebrovascular changes with repetitive exposure to blast.
The major goals are provided in statements of work in the next section.

15. SUBJECT TERMS brain inflammation; chronic, repetitive blast exposure; neuroinflammation; cerebrovascular changes; low-intensity blast overpressure exposure;

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
Unclassified	Unclassified	Unclassified	Unclassified	27	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

Accomplishments:

What were the major goals of the project?

The effort will examine the role of brain inflammation in response to chronic, repetitive blast exposure in active-duty military populations, veterans, and in an established animal model. The program will use multiple blood-based tests as well as brain imaging, which may be used in the future for detection and treatment of neurological injury in individuals with repetitive blast exposure. The program consists of four distinct projects examining the role of neuroinflammation in the manifestation of physiological and neurological sequalae resulting from repetitive low-intensity blast overpressure exposure.

Project 1: Exploring neuroinflammation in blast-exposed operational personnel.

Project 2: Neuroinflammation in Active-Duty SM with Diagnosed TBI.

Project 3: Neuroinflammation in Veterans with Diagnosed, Chronic TBI.

Project 4: Understanding the interplay between neuroinflammation and cerebrovascular changes with repetitive exposure to blast.

The major goals are provided in statements of work in the next section.

What was accomplished under these goals?

This program completed first year. The stated objectives in the beginning of this focused program award (FPA) are to fully develop and submit the human and animal protocols for institutional review with the aim to achieve approval in the near-term noting that approval for these processes reflects a complex dynamic between the institutional committees and the respective principal investigators. As this is the case it is not possible to precisely estimate or predict when approvals will be granted.

The FPA PI is working on establishing a multi-party cooperative research and development agreement (CRADA) with all institutions involved in this FPA. A draft of the agreement was sent by the PI's organization (in September 2023) to all parties for their review.

Project 1: Exploring neuroinflammation in blast-exposed operational personnel. (Project lead: Dr. James Stone, University of Virginia, UVA)

Completed:

- UVA IRB protocol has been approved.
- Second level approval through OHRO(Office of Human Research Oversight) has been granted for all qualified participants except for SOCOM subjects
- Cognitive testing and blood draw supplies have been acquired.
- Radiopharmaceutical production of [18F]DPA-714 has been optimized for study
- 50 subjects have been screened for the study, with 43 meeting inclusion criteria and 7 not meeting criteria.

Planned for next quarter:

- Subject prescreening and enrollment will continue.
- Subject procedures will commence.
- UVA IRB/OHRO approvals will be requested for the recruitment of SOCOM subjects.

Statement of Work (Project 1)

Specific Aim 1: Examine the association of neuronal-derived extracellular vesicles (NDEVs) and microglia-derived extracellular vesicles (MDEVs) protein markers of inflammation (IL-1β, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, CRP, TNF-a, and VEGF) and neurodegeneration (tau, p-tau, NfL, amyloid-beta 40/42) with prior blast exposure in active duty and veteran operational personnel a history of repetitive low-level blast exposure.	**Timeline**	**Completion %**	**Description**
Major Task 1 IRB/HRPO approval for planned research	Months		
Subtask 1 – Write UVA IRB protocol and achieve approval for planned work, referencing existing UVA RDRC protocol for use of [^{18}F]-DPA-714 in service members.	1	100%	
Subtask 2 – Human Subjects Research Protection Office (HRPO) review and approval of human subjects' protocol.	2-4	100%	
Milestone(s) Achieved: Human subjects protocol approved by UVA IRB and HRPO			Completed
Major Task 2 Recruitment, screening, and consent of service members into research study	Months		
Subtask 1 – Coordinate recruitment of special operators with SOCOM as well as with other blast exposed operational communities.	5-45	50%	Letter of support obtained from SOCOM
Subtask 2 – Perform blast history, head injury history, medical history, and MRI screening to assess for inclusion/exclusion from study.	5-45		
Subtask 3 – Perform informed consent for subjects who are candidates for participation in study.	5-45		
Milestone(s) Achieved: Successful recruitment, screening, and consent of subjects for research study.			
Major Task 3 Explore whether inflammatory and neurodegeneration biomarkers from NDEVs and MDEVs demonstrate a positive correlation with BETS/GBEV measures of prior blast exposure in operational personnel.	Months		
Subtask 1 – Acquisition of serum samples from service members for analysis of NDEVs and MDEVs protein markers.	5-45		
Subtask 2 – Analysis of serum samples acquired from service members for analysis of NDEVs and MDEVs protein markers, of inflammation (IL-1β, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, CRP, TNF-a, and VEGF) and neurodegeneration (tau, p-tau, NfL, amyloid-beta 40/42).	5-48		
Subtask 3 – Administer BETS and calculate GBEV for structured determination of prior blast exposure history.	5-45		
Subtask 4 – Examine relationships amongst NDEVs, MDEVs, and prior blast exposure history.	6-48		

Milestone(s) Achieved: Acquisition and analysis of serum samples from all participating service members, administration of BETS with calculation of GBEV for blast history determination, and assessment of relationship between serum biomarkers and prior blast exposure history.			

Specific Aim 2: Examine the association of neuroimaging measures of inflammation through PET-CT imaging of [18F]DPA-714 with prior blast exposure in active duty and veteran operational personnel with a history of repetitive low-level blast exposure.	**Timeline**	**Completion %**	**Description**
Major Task 4 Production of [^{18}F]DPA-714 neuroinflammation imaging ligand	Months		
Subtask 1 – Production of precursor for DPA-714	5-45		
Subtask 2 – Labeling of DPA-714 with ^{18}F	5-45		
Milestone(s) Achieved: Production of [^{18}F]DPA-714 imaging ligand			
Major Task 5 Perform PET-CT neuroimaging of [^{18}F]DPA-714 neuroinflammation imaging ligand	Months		
Subtask 1 – Acquire PET-CT neuroimaging of [^{18}F]DPA-714 neuroinflammation in service members.	5-45		
Milestone(s) Achieved: Successful acquisition of PET-CT neuroimaging of [^{18}F]DPA-714 neuroinflammation in service members.			
Major Task 6 Assess whether neuroimaging measures of inflammation will demonstrate a positive correlation with BETS/GBEV measures of prior blast exposure in operational personnel with a history of repetitive low-level blast exposure.	Months		
Subtask 1 – Examine relationships between [^{18}F]DPA-714 neuroimaging measures of inflammation and history of blast exposure as assessed by BETS and the calculated GBEV.	5-48		
Milestone(s) Achieved: Successful production of neuroinflammation imaging ligand, imaging of uptake in Active Duty and Veteran service members, and assessment of the relationship of neuroinflammation imaging ligand with prior history of blast exposure.			

Specific Aim 3: Explore relationships amongst NDEVs and MDEVs protein markers of inflammation (IL-1β, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, CRP, TNF-a, and VEGF) and neurodegeneration (tau, p-tau, NfL, amyloid-beta 40/42) with prior history of blast exposure, neuroimaging measures of inflammation through PET-CT imaging of [18F]-DPA-714, and structural and functional magnetic resonance imaging (MRI).	**Timeline**	**Completion** %	**Description**

Major Task 7 Perform MRI acquisitions on service members enrolled in research study	Months		
Subtask 1 - Acquire MRI sequences to assess for changes in white matter integrity (Diffusion Tensor Imaging [DTI]).	5-45		
Subtask 2 - Acquire MRI sequences to assess for changes in brain volume (3D-T1-weighted imaging)	5-45		
Subtask 3 - Acquire MRI sequences to assess for changes in functional connectivity (Blood Oxygen Level Dependent [BOLD] imaging)	5-45		
Subtask 4 - Acquire MRI sequences to assess for changes in brain perfusion (arterial spin labeling [ASL])	5-45		
Subtask 5 - Acquire MRI sequences for assess for presence of microhemorrhage (Susceptibility Weighted Imaging [SWI])	5-45		
Milestone(s) Achieved: Successful acquisition of MRI sequences to assess changes in white matter integrity, brain volume, brain connectivity, perfusion, and microhemorrhage.			
Major Task 8 Assess whether NDEVs/MDEVs and neuroimaging measures of neuroinflammation correlate with elevations in NDEVs/MDEVs measures of neurodegeneration and changes in brain structure and function as demonstrated by MRI.	Months		
Subtask 1 – Examine the relationships between NDEVs/MDEVs measures of neuroinflammation and neuroimaging measures of neuroinflammation.	6-48		
Subtask 2 – Assess relationships between NDEVs/MDEVs measures of neurodegeneration and changes in brain structure and function as demonstrated by MRI.	6-48		
Subtask 3 – Explore relationships amongst neuroimaging and serum biomarker measures of neuroinflammation, neurodegeneration, and brain structure and function	6-48		
Milestone(s) Achieved: Examination of relationships amongst NDEVs/MDEVs measures of neuroinflammation/neurodegeneration and neuroimaging measures of neuroinflammation and changes in brain structure and function in service members.			
Major Task 9 Examine whether a positive correlation will be observed between fluid biomarker and neuroimaging measures of neuroinflammation in operational personnel with a history of repetitive blast exposure.	Months		
Subtask 1 – Explore relationship between prior history of blast exposure, fluid biomarker/neuroimaging measures of inflammation and fluid biomarker/neuroimaging measures of neurodegeneration and changes in brain	6-48		

structure/function in service members participating in study.			
Milestone(s) Achieved: Examination of relationship between prior history of blast exposure, fluid biomarker/neuroimaging measures of inflammation and fluid biomarker/neuroimaging measures of neurodegeneration and changes in brain structure/function in service members participating in study.			
Specific Aim 4: Develop joint statistical model relating measures of neuroinflammation, brain structure and function, cognitive measures, and neurological symptoms using Similarity driven Multiview Linear Reconstruction (SiMLR).	**Timeline**	**Completion %**	**Description**
Major Task 10 Perform questionnaire and cognitive/neuropsychological assessments of service members participating in study.	Months		
Subtask 1 – Acquire demographic deployment exposure and injury characteristics assessments, including the Combat Exposure Scale (CES) and Blast Exposure Threshold Survey (BETS).	5-45		
Subtask 2 – Perform neuropsychological testing utilizing the California Verbal Learning Test – III, Delis-Kaplan Function System Verbal Fluency Test (DKEFS-VFT), and the NIH Toolbox Cognition Battery (NIHTB-CB).	5-45		
Subtask 3 – Assess psychological, post-concussive, and other health symptoms utilizing the Alcohol Use Disorders Identification Test Consumption Questions (AUDIT-C), Drug Abuse Screening Test-10 (DAST-10), Patient Health Questionnaire-9 (PHQ-9_, Generalized Anxiety Disorder-7 (GAD-7), PTSD Checklist for DSM-5 (PCL-5_, Headache Impact Test-6 (HIT-6), TBI Quality of Life (TBI-QOL) Pain Interference Short form, Neurobehavioral Symptom Inventory (NSI) 22, Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Psychological General Well-Being Index (PGWI).	5-45		
Subtask 4 – Assess performance validity utilizing the Test of Memory Malingering (TOMM).	5-45		
Milestone(s) Achieved: Successful acquisition of questionnaire and cognitive/neuropsychological assessments of service members participating study.			
Major Task 11 Develop model relating degree of blast exposure to level of neuroinflammation, changes in brain structure and function, increases in symptom reporting, and cognitive performance.	Months		
Subtask 1 – Perform template-based registration of all imaging data acquired for study.	5-48		
Subtask 2 – Import all imaging data into multi-dimensional matrix for joint analysis.	5-48		

Subtask 3 – Import all non-imaging data into multi-dimensional matrix for joint analysis.	5-48		
Subtask 4 – Develop model relating blast exposure to level of neuroinflammation, changes in brain structure and function, increases in symptom reporting, and cognitive performance.	5-48		
Milestone(s) Achieved: Successful development of model relating degree of blast exposure to level of neuroinflammation, changes in brain structure and function, increases in symptom reporting, and cognitive performance.			
Major Task 12 Reporting and data archiving	Months		
Subtask 1 – Quarterly reporting	4-48	100%	up to this quarter
Subtask 2 – Annual reporting	12-48	100%	1st annual report
Subtask 3 – FITBIR investigator and study registration	1		
Subtask 4 – Annual FITBIR data submissions	12-48		
Subtask 5 – Engage in research team meetings, including annual meetings with TBIPHRP Science Officer.	1-48	100%	up to this quarter
Milestone(s) Achieved: Successful study reporting and data archiving			

Project 2: Neuroinflammation in Active-Duty SM with Diagnosed TBI (Project lead: Dr. Jessica Gill, Johns Hopkins University, JHU)

Completed:

- Received guidance from OHRO on the way forward for handling and processing samples acquired from other human subject's research protocols mentioned in this FPA. JHU will not have an IRB protocol. However, JHU will establish reliance agreements with the protocols that are (or will be) approved at the three participating sites (UVA, University of Utah (UU), and National Military Center Camp Lejeune (NMCCL)) to receive and handle deidentified samples from these institutions. The JHU PI has requested the local IRB to initiate reliance agreement with UVA which will be followed by similar action with the remaining two institutions.

Planned for next quarter:

- Follow-up with JHU IRB on establishing reliance agreements with:
  UVA (currently in process)
  NMCCL (to be initiated)
  UU (pending approvals for local IRB protocols)

Statement of work (Project 2)

The SOW for project 2 is being modified based on OHRO's guidance to establish reliance agreements between Johns Hopkins University (JHU) and the IRB protocols at UVA, UU, NMCCL. These changes are indicated below.

JHU will receive deidentified samples from the three institutions above and will not carry out any subject recruitment.

Study Aim 1: Examine brain-derived extracellular vesicles (BDEVs) and microglia-derived extracellular vesicles (MDEVs) protein markers of inflammation (IL-1β, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, CRP, TNFα, and VEGF) and neurodegeneration (tau, p-tau, NfL, amyloid-beta 40/42) within ~~24 hours of injury~~, 3-months and 6 months, and 1-year follow-up in SMs with an acute mTBI (n=50) and healthy control (n=50). **Major Task 1:** Examine neuron and microglia specific proteins and makers of inflammation (of IL-1β, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, CRP, TNF-a, TGF-beta and GM-CSFand VEGF) and neurodegeneration (tau, p-tau, NFL, amyloid-beta 40/42) in SMs with (n=50) and without (n=50) with an acute TBI.	**Timeline**	**Completion %**	**Description**
Subtask 1 – Complete needed regulatory documents to obtain samples from UVA, UU, and NMCCL ~~sweat samples and clinical data~~: • ~~Approval of an exempt protocol at Johns Hopkins to obtain sweat samples and de-identified clinical data, including neuro-imaging files and sleep studies~~ • ~~Obtain HRPO approval of study activities~~ • ~~Develop a material transfer request between Johns Hopkins University and UVA's SOCOM pilot study~~ • ~~Develop a research consortium agreement among all investigators included at Johns Hopkins University, UVA~~ • Establish reliance agreements between JHU and IRB protocols at • 1) UVA	1-3		In process

• 2) UU • 3) NMCCL			
Subtask 2- Prepare for experiments. • Place orders for all needed laboratory reagents and supplies • Develop a standard operating procedure for all assays to be undertaken within this project. • Training and standardization of all processes and procedures within the laboratory to establish and maintain quality standards	2-4	50%	
Subtask 3- ~~Accrue subjects~~Sample storage • ~~Recruit up to 8 subjects per month~~ • ~~Obtain consent in IRB approved manner~~ • ~~Collect baseline data: severity of TBI, type of TBI, if blast- severity, number of previous blasts and TBIs, acute symptoms (NSI), current medications and diagnoses receiving treatment, and demographic characteristics~~ • ~~Collect acute~~ ~~blood samples~~ • Receive ,process and store blood samples in a deidentified process	4-34		
~~Subtask 4- Follow subjects over time~~ • ~~Maintain contact with subjects to schedule return appointments via phone and email~~ • ~~Collect follow-up data at 3, 6, and 12months~~	4-34		
Subtask 4 ~~5~~- Measurement of proteins in blood and exosomes • Develop and implement a team of laboratory staff to undertake assays 2-3 days per week. • Develop and implement quality control measures to review data as it is generated. • Undertake re-run of assays that do not meet quality of quantification standards- coefficient of variation greater than 20%	12-36		
Milestone(s) Achieved: Laboratory data will be generated in circulation on proteins included in the aim, using a high standard for quality and completeness			
Study Aim 2: Examine the association of BDEVs and MDEVs protein markers of inflammation (IL-1β, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, CRP, TNF-a, and VEGF) and neurodegeneration (tau, p-tau, NfL, amyloid-beta 40/42) with neurological (NSI) and psychological symptoms (PCL-5, PHQ9). **Major Task 2:** Determine if previous blast exposure relates to higher acute levels of neuron and microglia specific proteins bio-makers of inflammation (of IL-1β, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, CRP, TNF-a, TGF-beta and GM-			

CSF and VEGF) and neurodegeneration (tau, p-tau, NFL, amyloid-beta 40/42), and to risk for neurological (NSI) or psychological symptoms (PCL-5, PHQ9) at 3, 6, and 12 months following a TBI.			
Subtask 1-Develop a pipeline for analyses of symptoms and biomarkers. • Standardization of continuous and categorical data generation • Merging of clinical data with biomarkers • Analyses to examine links of biomarkers to symptoms, while considering covariates and other variables that may relate to these relationships	1-3		
Subtask 2- Combine clinical data to biomarker data. • Undertake quality review of clinical and laboratory data. • Determine possible reasons for missing data and ways to address in coordination with the clinical team. • Develop grouping variables based on clinical and diagnostic criteria	20-36		
Study Aim 3: Determine if previous blast exposure relates to higher acute levels of BDEVs and MDEVs protein biomarkers of inflammation (IL-1β, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, CRP, TNF-a, and VEGF) and neurodegeneration (tau, p-tau, NfL, amyloid-beta 40/42), and to risk for neurological (NSI) or psychological symptoms (PCL-5, PHQ9) 3 and 6 months following a TBI. **Major Task 3:** Determine if: 1) SMs with previous blast exposure will be related to higher neurobehavioral and psychological symptoms, and 2) SMs with the highest third of previous blast exposures will have greater concentrations of inflammatory and neurodegeneration markers from BDEVs and MDEVs compared to SMs within the lowest third of previous blast exposures.			
Subtask 1- Undertake Analyses • Examine variation in data and possible outliers through visual examination methods. • Create categorical variables based on clinical criteria and percentiles of data. • Build regression models to determine prediction values will abiding by assumptions. • Determine possible covariates, and requirements for inclusion within models	12-48		
Study Aim 4: Develop joint statistical model relating measures of neuroinflammation, cognitive measures, and neurological symptoms using Similarity driven Multiview Linear Reconstruction (SiMLR)			

Major Task 4: Develop a model, which relates degree of blast exposure to level of neuroinflammation, increases in symptom reporting, and cognitive performance following TBI in SMs with prior history of blast exposure. This model can be used to identify blast exposure thresholds in the setting of acute TBI, above which increases in BDEVs and MDEVs along with increases in symptom reporting and decrements in cognitive performance are observed.	12-48		
Subtask 1- Develop a statistical model relating measures of neuroinflammation, cognition, and neurological symptoms using SiMLR.	12-36		
Subtask 2- Identify blast exposure thresholds in the setting of acute TBI, above which increases in BDEVs and MDEVs along with increases in symptom reporting and decrements in cognitive performance are observed.	24-48		
Milestone(s) Achieved: Joint statistical model developed.			
Major Task 5: Reporting and data archiving	Months		
Subtask 1 – Quarterly reporting	4-48	100%	up to this quarter
Subtask 2 – Annual reporting	12-48	100%	1st annual report
Subtask 3 – FITBIR investigator and study registration	1-6		
Subtask 4 – Annual FITBIR data submissions	12-48		
Milestone(s) Achieved: Successful study reporting and data archiving			

Project 3: Neuroinflammation in Veterans with Diagnosed, Chronic TBI. (Project lead: Dr. Elisabeth Wilde, University of Utah, UU)

Completed:

- IRB protocols submitted to University of Utah and Salt Lake City Veterans Affairs (SLC VA).
- All testing materials have been acquired and folders prepared.
- Completed training with project staff on recruitment procedures and testing and imaging.
- New staff have completed required phlebotomy training and general blood processing training.
- The PI and staff have been working on a regulatory binder and standard operating procedure manual for this project.
- The PI and staff have been in communication with the Physical Medicine & Rehabilitation Services and Neurology careline chiefs at the Veteran Affairs regarding recruitment procedures from their clinics as well as access to a registry that has been kept for patients with TBI over the last 10 years.

Planned for next quarter:

- Follow up on local approval of IRB protocol(s)
- Training on blood processing procedures specific to this project

- The PI and staff have set up the project with UU radiology and will be testing the protocol, given our upgrade to Prisma software XA30. The protocol is well established, and we do not anticipate any issues.

Statement of Work (Project 3)

Specific Aim 1: Examine the association of neuronal-derived extracellular vesicles (NDEVs) and microglia-derived extracellular vesicles (MDEVs) protein markers of inflammation (IL-1β, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, CRP, TNF-α, and VEGF) and neurodegeneration (tau, p-tau, NfL, amyloid-beta 40/42) in Veterans with clinically-diagnosed TBI and prior blast exposure as compared to matched controls.	**Timeline**	**Completion %**	**Description**
Major Task 1 IRB/HRPO approval for planned research	Months		
Subtask 1 – Write local IRB protocol (UU and VA), submit VA RR&D application, and achieve approval for planned work.	1	80%	In process
Subtask 2 – Human Subjects Research Protection Office (HRPO) review and approval of human subjects' protocol.	2-4		
Milestone(s) Achieved: Human subjects protocol approved by local IRB and HRPO			
Major Task 2 Recruitment, screening, and consent of Veteran participants into research study	Months		
Subtask 1 – Enroll Veterans with TBI and controls into study	5-33		
Subtask 2 – Perform blast history, head injury history, medical history, and MRI screening to assess for inclusion/exclusion from study.	5-33		
Subtask 3 – Perform informed consent for subjects who are candidates for participation in study.	5-33		
Milestone(s) Achieved: Successful recruitment, screening, and consent of subjects for research study.			
Major Task 3 Explore whether inflammatory and neurodegeneration biomarkers from NDEVs and MDEVs demonstrate a positive correlation with BETS/GBEV measures of prior blast exposure in Veterans with clinically-diagnosed TBI and as compared to matched controls.	Months		
Subtask 1 – Acquisition of serum samples from Veterans for analysis of NDEVs and MDEVs protein markers.	5-33		
Subtask 2 – Analysis of serum samples acquired from Veterans for analysis of NDEVs and MDEVs protein markers, of inflammation (IL-1β, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, CRP, TNF-α, and VEGF) and neurodegeneration (tau, p-tau, NfL, amyloid-beta 40/42).	5-35		
Subtask 3 – Administer BETS and calculate GBEV for structured determination of prior blast exposure history.	5-33		
Subtask 4 – Examine relationships amongst NDEVs, MDEVs, and prior blast exposure history.	6-35		

Milestone(s) Achieved: Acquisition and analysis of serum samples from all participating Veterans, administration of BETS with calculation of GBEV for blast history determination, and assessment of relationship between serum biomarkers and prior blast exposure history.			
Specific Aim 2: Explore relationships amongst NDEVs and MDEVs protein markers of inflammation (IL-1β, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, CRP, TNF-a, and VEGF) and neurodegeneration (tau, p-tau, NfL, amyloid-beta 40/42) with prior history of blast exposure, and structural and functional magnetic resonance imaging (MRI) in Veterans with clinically symptomatic TBI and prior blast exposure vs. matched controls.	**Timeline**	**Completion %**	**Description**
Major Task 4 Perform MRI acquisitions on Veterans enrolled in research study; organize and transfer data to UVA	Months		
Subtask 1 - Acquire MRI sequences to assess for changes in white matter integrity (diffusion tensor imaging [DTI]).	5-33		
Subtask 2 - Acquire MRI sequences to assess for changes in brain volume (3D-T1-weighted imaging)	5-33		
Subtask 3 - Acquire MRI sequences to assess for changes in functional connectivity (Blood Oxygen Level Dependent [BOLD] imaging)	5-33		
Subtask 4 - Acquire MRI sequences to assess for changes in brain perfusion (arterial spin labeling [ASL])	5-33		
Subtask 5 - Acquire MRI sequences for assess for presence of microhemorrhage (Susceptibility Weighted Imaging [SWI])	5-33		
Milestone(s) Achieved: Successful acquisition of MRI sequences to assess changes in white matter integrity, brain volume, brain connectivity, perfusion, and microhemorrhage.			
Major Task 5 Assess whether NDEVs/MDEVs and neuroimaging measures of neuroinflammation correlate with elevations in NDEVs/MDEVs measures of neurodegeneration and changes in brain structure and function as demonstrated by MRI.	Months		
Subtask 1 – Examine the relationships between NDEVs/MDEVs measures of neuroinflammation and neuroimaging measures of neuroinflammation.	6-35		
Subtask 2 – Assess relationships between NDEVs/MDEVs measures of neurodegeneration and changes in brain structure and function as demonstrated by MRI.	6-35		
Subtask 3 – Explore relationships amongst neuroimaging and serum biomarker measures of neuroinflammation, neurodegeneration, and brain structure and function	6-35		
Milestone(s) Achieved: Examination of relationships amongst NDEVs/MDEVs measures of			

neuroinflammation/neurodegeneration and neuroimaging measures of neuroinflammation and changes in brain structure and function in Veterans with prior history of blast exposure and TBI vs. controls.			
Major Task 6 Examine whether a positive correlation will be observed between fluid biomarker and neuroimaging measures of neuroinflammation in operational personnel with a history of repetitive blast exposure.	Months		
Subtask 1 – Explore relationship between prior history of blast exposure, fluid biomarker/neuroimaging measures of inflammation and fluid biomarker/neuroimaging measures of neurodegeneration and changes in brain structure/function in Veterans participating in study.	6-35		
Milestone(s) Achieved: Examination of relationship between prior history of blast exposure, fluid biomarker/neuroimaging measures of inflammation and fluid biomarker/neuroimaging measures of neurodegeneration and changes in brain structure/function in Veterans participating in study.			
Specific Aim 3: Develop joint statistical model relating measures of neuroinflammation, brain structure and function, cognitive measures, and neurological symptoms using Similarity driven Multiview Linear Reconstruction (SiMLR).	**Timeline**	**Completion %**	**Description**
Major Task 7 Perform questionnaire and cognitive/neuropsychological assessments of Veterans participating in study.	Months		
Subtask 1 – Acquire demographic deployment exposure and injury characteristics assessments, including the Combat Exposure Scale (CES) and Blast Exposure Threshold Survey (BETS).	5-33		
Subtask 2 – Perform neuropsychological testing utilizing the California Verbal Learning Test – III, Delis-Kaplan Function System Verbal Fluency Test (DKEFS-VFT), and the NIH Toolbox Cognition Battery (NIHTB-CB).	5-33		
Subtask 3 – Assess psychological, post-concussive, and other health symptoms utilizing the Alcohol Use Disorders Identification Test Consumption Questions (AUDIT-C), Drug Abuse Screening Test-10 (DAST-10), Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder-7 (GAD-7), PTSD Checklist for DSM-5 (PCL-5), Headache Impact Test-6 (HIT-6), TBI Quality of Life (TBI-QOL) Pain Interference Short form, Neurobehavioral Symptom Inventory (NSI) 22, Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Psychological General Well-Being Index (PGWI).	5-33		
Subtask 4 – Assess performance validity utilizing the Test of Memory Malingering (TOMM).	5-33		

Milestone(s) Achieved: Successful acquisition of questionnaire and cognitive/neuropsychological assessments of Veterans participating in study.			
Major Task 8 Develop model relating degree of blast exposure to level of neuroinflammation, changes in brain structure and function, increases in symptom reporting, and cognitive performance.	Months		
Subtask 1 – Perform template-based registration of all imaging data acquired for study.	5-35		
Subtask 2 – Import all imaging data into multi-dimensional matrix for joint analysis.	5-35		
Subtask 3 – Import all non-imaging data into multi-dimensional matrix for joint analysis.	5-35		
Subtask 4 – Develop model relating blast exposure to level of neuroinflammation, changes in brain structure and function, increases in symptom reporting, and cognitive performance.	5-35		
Milestone(s) Achieved: Successful development of model relating degree of blast exposure to level of neuroinflammation, changes in brain structure and function, increases in symptom reporting, and cognitive performance.			
Major Task 9 Reporting and data archiving	Months		
Subtask 1 – Quarterly reporting	4-36	100%	up to this quarter
Subtask 2 – Annual reporting	12-36		
Subtask 3 – FITBIR investigator and study registration	1		
Subtask 4 – Annual FITBIR data submissions	12-36		
Milestone(s) Achieved: Successful study reporting and data archiving			

Project 4: Understanding the interplay between neuroinflammation and cerebrovascular changes with repetitive exposure to blast. (Project leads: Dr. Rania Abutarboush and Dr. Usmah Kawoos, Naval Medical Research Command, NMRC)

Completed:

- All approvals received to commence animal work.
- Staff trained to conduct specialized surgical procedures involved in the project.
- Animal work: 85 animals under aims 1 and 2 were exposed to blast/sham conditions for 30-day and 365-day post-blast time points.
- Tissue was harvested from animals in 30-day post-blast time point under both aims. The samples will be utilized in molecular assays.

Planned for next quarter:

- Continue animal experiments including intravital microscopy to assess cerebrovascular reactivity.

Statement of Work (Project 4)

Specific Aim 1: Assess neuroinflammation and changes in cerebrovascular reactivity and neurodegeneration in an established model of repetitive low-level blast in a time-course study to understand the short- and long-term effects of repetitive blast exposure.	**Timeline**	**Completion %**	**Description**

Major Task 1 Hypothesis to be tested: Neuroinflammatory changes will correlate with altered cerebrovascular reactivity.	Months		
Subtask 1 –Preparation of animal use protocol and submission to NMRC's Institutional Animal Care and Use Committee for review and approval. Submission to ACURO for review. Protocol initiation meeting with the members of IACUC and Veterinary Service Providers team to be able to begin animal work.	1-4	100%	
Milestone # 1: IACUC and ACURO approvals obtained for animal use protocol.	1-4	100%	Completed
Subtask 2- Intravital microscopy (IVM) experiments for assessing cerebrovascular reactivity and perform assays to evaluate blast-related neuroinflammatory response and vascular changes for post-exposure time points 7, 14, and 30 days (120 animals total) in rats (Rattus Norwegicus)	5-15		Personnel trained on performing the procedures
Subtask 2a: Conduct IVM assessment of cerebrovascular reactivity in sham and blast-exposed animals at 7, 14, and 30 days post-exposure. 10 rats/group- 60 rats total.	5-12		
Subtask 2b: Expose animals to blast or sham conditions and harvest biospecimens at 7, 14, 30 days post-exposure (blast or sham) for performing molecular assays. 10 rats/group- 60 rats total.	6-12	33%	Specimens harvested from 20 animals in 30-day group
Milestone # 2: Completion of IVM experiments and tissue collection for molecular assays for time points 7, 14, and 30 days post-blast.	5-12		
Subtask 2c: Perform molecular assays to assess changes in pro-inflammatory factors, cytokines, various markers of vascular integrity and neurodegeneration.	9-15		
Milestone # 3: Completion of molecular assays for time points 7, 14, and 30 days post-blast.	9-15		
Subtask 3- IVM experiments for assessing cerebrovascular reactivity and perform assays to evaluate blast-related neuroinflammatory response and vascular changes for post-exposure chronic time point (365 days). 10 rats/group- 20 rats for IVM and 20 rats for molecular assays- 40 rats total.	7-21	40%	30 animals exposed to blast/sham conditions
Milestone # 4: Completion of IVM experiments and molecular assays for 365 day post-blast.	7-21		
Milestone # 5: Report data on the short-and long-terms effects of repetitive low-level blast on cerebrovascular reactivity, neuroinflammatory responses, and vascular changes.	21-24		
Milestone(s) Achieved: 1. Approved IACUC protocol. 2. Completion of time course study to understand the short- and long-term effects of repetitive low-level blast on cerebrovascular reactivity using IVM.			

3. Completion of molecular assays to evaluate the vascular changes and inflammatory responses to repetitive low-level blast exposures over the time course of 365 days at pre-determined time points. 4. Correlation between cerebrovascular reactivity and inflammatory responses to repetitive low-level blast exposures is determined.			
Specific Aim 2: Assess the effect of modulation of neuroinflammation by pharmacological blocking of ADAM17 on cerebrovascular reactivity in a model of repetitive low-level blast.			
Major Task 2 Hypothesis to be tested: Inhibition of the ADAM17 pathway will result in decrease in pro-inflammatory TNF-α and other pro-inflammatory factors (e.g., IL-6) and modulation of cerebrovascular reactivity following repetitive low-level blast.	Months		
Subtask 1- Assessment of cerebrovascular reactivity at 7, 14, and 30 days post-blast using IVM and neuroinflammatory response and vascular changes using molecular assays after treatment with an ADAM17 inhibitor. 120 rats total.	13-23		
Subtask 1a: Conduct IVM assessment of cerebrovascular reactivity in sham and blast-exposed animals at 7, 14, and 30 days post-exposure. 10 rats/group- 60 rats total.	13-20		
Subtask 1b: Expose animals to blast or sham conditions and harvest biospecimens at 7, 14, 30 days post-exposure (blast or sham) for performing molecular assays. 10 rats/group- 60 rats total.	14-20	33%	Specimens harvested from 20 animals in 30-day group
Milestone # 6: Completion of IVM experiments and tissue collection for molecular assays for time points 7, 14, and 30 days post-blast and treatment with ADAM17 inhibitor.	13-20		
Subtask 1c: Perform molecular assays to assess changes in pro-inflammatory factors, cytokines, various markers of vascular integrity and neurodegeneration.	17-23		
Milestone # 7: Completion of molecular assays for time points 7, 14, and 30 days post-blast and treatment with ADAM17 inhibitor.	17-23		
Subtask 2- IVM experiments for assessing cerebrovascular reactivity and perform assays to evaluate blast-related neuroinflammatory response and vascular changes for post-exposure chronic time point (365 days). 10 rats/group- 20 rats for IVM and 20 rats for molecular assays- 40 rats total.	19-34	20%	15 animals exposed to blast/sham conditions
Milestone # 8: Completion of IVM experiments and molecular assays for 365 day post-blast and treatment with ADAM17 inhibitor.	19-34		
Milestone(s) Achieved:			

1. Completion of time course study to understand the effect of modulation of neuroinflammation by pharmacological blocking of ADAM17 on cerebrovascular reactivity using IVM in repetitive low-level blast model. 3. Completion of molecular assays to evaluate the vascular changes and inflammatory responses to repetitive low-level blast exposures after treatment with ADAM17 inhibitor. 4. Correlation between modulation of inflammatory responses and cerebrovascular reactivity in a repetitive low-level blast exposure model is determined.			
Milestone # 9: Report data on the effect of modulation of neuroinflammation by pharmacological blocking of ADAM17 on cerebrovascular reactivity in a model of repetitive low-level blast.	34-36		
Milestone #10: Prepare final report for entire study and manuscripts for publication in peer-reviewed journals.	34-36		

Describe the Regulatory Protocol and Activity Status (if applicable).

(a) Human Use Regulatory Protocols

PROTOCOL(S):

Protocol (1 of 3 total):

Protocol: approved

Title: Evaluation of the Bio-Effects of Repeated, Low-Level Blast using PET CT

Target required for clinical significance: 120

Target approved for clinical significance: 120

This protocol will support projects 1 and 2 of FPA.

Submitted to and Approved by:

- UVA IRB, approved 23 Sep 2022
- OHRO, approved 01 May 2023

Status:

UVA IRB approval 23 Sep 2022, OHRO limited approval (log # E03732.1a) May 1, 2023. Approval limited to recruitment of non-SOCOM members obtained in May 2023. We are working with USSOCOM and OHRO to meet the requirements for enrolling SOCOM participants.

TOTAL PROTOCOLS: 3

PROTOCOL (1 of 3 total):

Protocol: IRB and OHRO approvals obtained

Title: Evaluation of the Bio-Effects of Repeated, Low-Level Blast using PET CT

Target required for clinical significance: 120

Target approved for clinical significance: 120

SUBMITTED TO AND APPROVED BY:

- UVA IRB, approved 23 Sep 2022
- OHRO, approved 01 May 2023

STATUS:

(i) Number of subjects recruited/original planned target: 43 recruited
Number of subjects screened/original planned target: 50
Number of patients enrolled/original planned target: 43
Number of patients completed/original planned target: NA

(ii) Report amendments submitted to the IRB and USAMRMC OHRO for review: NA

(iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation: NA

PROTOCOL(S):

Protocol (2 of 3 total):

Protocol: NA

Title: University of Utah and Salt Lake City Veterans Affairs human use protocol.

Target required for clinical significance:

Target approved for clinical significance:

This protocol will support projects 2 and 3 of FPA

Submitted to and Approved by:

- Submitted to University of Utah IRB and SLCVA IRB

Status:

Protocol submitted to the local IRB. Review and approval pending.

PROTOCOL (2 of 3 total):

Protocol: NA

Title: University of Utah human use protocol

Target required for clinical significance:

Target approved for clinical significance:

SUBMITTED TO AND APPROVED BY:

- Submitted to University of Utah IRB

STATUS:

(i) Number of subjects recruited/original planned target: NA
Number of subjects screened/original planned target: NA
Number of patients enrolled/original planned target: NA
Number of patients completed/original planned target: NA

(ii) Report amendments submitted to the IRB and USAMRMC OHRO for review: NA

(iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation: NA

Protocol (3 of 3 total):

Protocol: Actively running participants.

Title: Long-Term Outcomes following mTBI in a Military Population.

Target required for clinical significance: 39 mTBI, 39 control

Target approved for clinical significance: 50 mTBI, 50 control

This protocol will support project # 2 of FPA

Submitted to and Approved by:

- Approved by Naval Medical Center Camp Lejeune and Naval Medical Center Portsmouth Institutional Review Boards.

Status:

Actively recruiting and running participants.

PROTOCOL (3 of 3 total):

Protocol: Actively running participants.

Title: Long-Term Outcomes following mTBI in a Military Population.

Target required for clinical significance: 39 mTBI, 39 control

Target approved for clinical significance: 50 mTBI, 50 control

SUBMITTED TO AND APPROVED BY:

- Approved by Naval Medical Center Camp Lejeune and Naval Medical Center Portsmouth Institutional Review Boards.

STATUS:

(i) Number of subjects recruited/original planned target: 32 recruited
Number of subjects screened/original planned target: 25 (23 mTBI, 2 control)
Number of patients enrolled/original planned target: 25

T0 = 25 [23 mTBI, 2 control]
T1 = 14 complete [12 mTBI, 2 control]
T2 = 8 complete [8 mTBI]
T3 = 6 complete [6 mTBI]
T4 = 2 complete [2 mTBI]

(T0, T1, T2, .. are 3 months apart)

Number of patients completed/original planned target: 0

(ii) Report amendments submitted to the IRB and USAMRMC OHRO for review:
Amendment 1 – Approved 14MAR2019 – update protocol
Amendment 2 – Approved 20MAR2019 – Personnel change
Amendment 3 – Approved 24JUL2019 – Personnel change
Amendment 4 – Approved 22OCT2019 – Personnel change
Amendment 5 – Approved 31MAR2020 – Personnel change
Amendment 6 – Approved 05OCT2020 – Personnel change, study update
Amendment 7 – Approved 07JAN2021 – Personnel change, study update
Amendment 8 – Approved 27APR2021 – Study update (added BETS)
Amendment 9 – Approved 11JUN2021 – Study update
Amendment 10 – [Transfer to Naval Medical Center Portsmouth adjusted the numbering system. One amendment was considered the original protocol.]
Amendment 11 – [Transfer to Naval Medical Center Portsmouth adjusted the numbering system. One amendment was considered the Y1 Continuing Review.]
Amendment 12 – [Transfer to Naval Medical Center Portsmouth adjusted the numbering system. One amendment was considered the Y2 Continuing Review.]
Amendment 13 – [Transfer to Naval Medical Center Portsmouth adjusted the numbering system. One amendment was considered the Y3 Continuing Review.]
Amendment 14 – Approved 30DEC2021 – Contact information update
Amendment 15 – Approved 15FEB2022 – Update recruitment flyers
Amendment 16 – Approved 08MAR2022 – Add QR code to flyers
Amendment 17 – Approved 03MAY2022 – Update protocol
Amendment 18 – Approved 08SEP2022 – Update recruitment
Amendment 19 – Approved 27SEP2022 – Personnel change
Amendment 20 – Approved 29NOV2022 – Update questionnaires
Amendment 21 – Approved 13JAN2023 – Personnel change
Amendment 22 – Approved 24MAR2023 – Study update
Amendment 23 – Approved 19APR2023 – Personnel change
Amendment 24 – Approved 01SEP2023 – Personnel change

(iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation: 0

Use of Human Cadavers for Research Development Test & Evaluation (RDT&E), Education or Training

This research program does not utilize cadavers.

(c) Animal Use Regulatory Protocols

TOTAL PROTOCOL(S): 1

The institution performing research with animal subjects is:

The Naval Medical Research Command (PI: Dr. Rania Abutarboush)

PROTOCOL(S):

Protocol (1 of 1 total):

Protocol: Fully IACUC and ACURO approved.

Title: Understanding the complex interplay between neuroinflammation and cerebrovascular changes with repetitive exposure to blast in a rat (Rattus Norvegicus) model

Target required for statistical significance: 320

Target approved for statistical significance: 320

Submitted to and Approved by:

IACUC: 3/13/2023

ACURO: (protocol # TP210540.e001) approved on 3/30/2023

Status:

Fully IACUC and ACURO approved.

TOTAL PROTOCOL(S): 1

PROTOCOL (1 of 1 total):

Title: Understanding the complex interplay between neuroinflammation and cerebrovascular changes with repetitive exposure to blast in a rat (Rattus Norvegicus) model

Target required for statistical significance: 320

Target approved for statistical significance: 320

SUBMITTED TO AND APPROVED BY:

IACUC: 3/13/2023

ACURO: (protocol # TP210540.e001) approved on 3/30/2023

STATUS: Fully IACUC and ACURO approved.

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

Continue experiments.

Products:

Nothing to report.

Participants & Other Collaborating Organizations

What individuals have worked on the project?

Name:	Dr. Stephen Ahlers
Project Role:	FPA Overall PI
Nearest person month worked:	2.4
Contribution to Project:	Administrative and scientific oversight of the overall program

Name:	Dr. Rania Abutarboush
Project Role:	PI of NMRC animal study
Nearest person month worked:	1.2
Contribution to Project:	Developed, designed, and execution of animal study.

Name:	Dr. Usmah Kawoos
Project Role:	Administration of FPA/Co-Investigator of animal study
Nearest person month worked:	1.2
Contribution to Project:	Administration of FPA/Developed, designed, and execution of animal study together with Dr. Abutarboush

Name:	Dr. Ye Chen
Project Role:	Molecular biologist
Nearest person month worked:	0.6
Contribution to Project:	Assisted in preparation of animal protocol and identifying molecular assays.

Name:	Mr. Jonathan Statz
Project Role:	Biostatistician
Nearest person month worked:	0.6
Contribution to Project:	Performed statistical review of animal protocol

Name:	Dr. Jamila Asgar
Project Role:	Post-doctoral fellow
Nearest person month worked:	11
Contribution to Project:	Execution of animal study

Name:	Dr. Kapinga Ngalula
Project Role:	Scientist
Nearest person month worked:	1
Contribution to Project:	Execution of animal study

Name:	Dr. James Stone
Project Role:	UVA Site PI
Nearest person month worked:	1.13
Contribution to Project:	Developed, designed, and execution of PET CT study in Active Duty personnel

Name:	Dr. Nicholas Tustison
Project Role:	UVA-Medical imaging expertise
Nearest person month worked:	0.8

Contribution to Project: Assisted with study design

Name: Ms. Lyons
Project Role: UVA-Clinical Research Coordinator
Nearest person month worked: 12
Contribution to Project: Assisted with study protocol and coordination

Name: Dr. James Patrie
Project Role: UVA-Biostatistician
Nearest person month worked: 0.8
Contribution to Project: Assisted with study protocol

Name: Dr. Jessica Gill
Project Role: John Hopkins University School of Nursing Site PI
Nearest person month worked: 1.8
Contribution to Project: Developed, designed, and execution of study in Active Duty with diagnosed TBI

Name: Ms. Chelsea Wagner
Project Role: JHU- Lab director
Nearest person month worked: 12
Contribution to Project: Protocol development, submission, and tracking

Name: Ms. Katie Edwards
Project Role: JHU- Research Associate
Nearest person month worked: 12
Contribution to Project: Assistance with protocol preparation and submission

Name: Dr. Elizabeth Wilde
Project Role: University of Utah Site PI
Research Identifier: 0000-0002-9839-4428
Nearest person month worked: 1.8
Contribution to Project: General oversight of Project 3, including training/supervision of neuropsychological testing and imaging acquisition, regulatory issues and progress reports.

Name: Dr. David Tate, PhD
Project Role: UU-Co-Investigator
Researcher Identifier: 0000-0003-0213-1920
Nearest person month worked: 1.8
Contribution to Project: Supervision of screening and recruitment, audits of neuropsychological testing

Name: Mr. Tracy Abildskov
Project Role: UU- Staff
Nearest person month worked: 0.6
Contribution to Project: Imaging data transfer, organization, archive and storage

Name: Ms. Hilary Rusell, MA
Project Role: UU-Senior Project Coordinator
Nearest person month worked: 12
Contribution to Project: Creation of Standard Operating Procedure manual, ordering supplies, assisting in regulatory compliance, recruitment and screening, data collection (neuropsychology and imaging), meeting planning

Name: Ms. Karla Figueroa
Project Role: UU- Staff
Nearest person month worked: 0.6
Contribution to Project: Oversight of preparation of blood specimen collection, handling, and shipping

Name: Ms. Elizabeth Hovenden
Project Role: UU- Project Coordinator
Nearest person month worked: 12
Contribution to Project: Creation of Standard Operating Procedure manual, recruitment and screening, scheduling participants, data collection (neuropsychology, imaging and blood collection)

Name: Dr. Naomi Hunsaker, PhD
Project Role: UU-Research Associate
Nearest person month worked: 1.2
Contribution to Project: Preparation of imaging quality control and processing protocols.

Changes/Problems:

a. Actual Problems or delays and actions to resolve them

Extended delays were experienced under project 3 (at UU) for processing of IRB protocols. The protocol was submitted to the IRB 7 months ago at UU/SLC VA, but the VA changed their requirements substantially within the last year. The VA now requires a parallel VA IRBNet submission in addition to the regular VA RR&D requirements and UU IRB, which has been a big adjustment both for local VA regulatory staff as well as the team on project 3. Additionally, despite the fact that the only activity that will be performed at the VA is recruitment, the VA also recently changed its requirement regarding Data Use Agreements (DUA) between the local VA and the academic affiliate (this is now also a requirement for IRB approval). This introduced an additional step in the process needing significant input from the Central VA. The DUA is the final stages of review.

b. Anticipated Problems/Issues

Nothing to report.

Special Reporting Requirements:

Quad Charts: See Attached.