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TITLE: Autonomic Dysfunction, Brain Blood Flow, and Cognitive Decline in Veterans with Gulf War Illness

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<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b> The incidence of multi-symptom illness or Gulf War Illness (GWI) in the Veterans deployed during the Gulf War is estimated to be 25-32%. The primary goal of this project is to examine cerebral blood flow responses to chemical and metabolic stress in Veterans with GWI compared with age and deployment-matched Veterans. We hypothesize that GWI is associated with both vascular dysfunction in the cerebral circulation and autonomic dysfunction. Participants will take part in a laboratory visit for autonomic function testing, and a magnetic resonance imaging scan (MRI) visit to determine brain structure and intracranial blood flow measurements at rest and in response to physiological stress. These experiments represent a novel and comprehensive approach and address fundamental and significant unresolved physiological questions in how GWI affects the human brain, with relevance to GWI symptoms.					
<b>15. SUBJECT TERMS</b> Gulf War Illness; Middle Aged; Neuroimaging; Autonomic; Cerebral Blood Flow					
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## **1. Introduction**

The incidence of multi-symptom illness or Gulf War Illness (GWI) in the Veterans deployed during the Gulf War is estimated to be 25-32%. As Veterans from the Gulf War grow older, they may develop age-related conditions earlier and have a premature onset of disability. Importantly, many of the pathophysiological changes associated with GWI may increase the risk of developing Alzheimer's disease (AD) or other dementias. Altered regulation of cerebral blood flow is likely a key mechanism underlying the cognitive complaints in Veterans with GWI. In addition, autonomic dysfunction has been associated with GWI and this may be functionally linked to the impairment in cerebral blood flow regulation. Cerebral blood flow responses to chemical and metabolic stress will be measured in Veterans with GWI compared with age and deployment-matched Veterans. This project will be the first step in providing critical information and establish a proof-of-concept regarding the pathophysiology of GWI.

## **2. Keywords**

Gulf War Illness; Middle Aged; Neuroimaging; Autonomic; Cerebral Blood Flow

## **3. Accomplishments**

The major goals of this project include: (1) to determine if Veterans with GWI demonstrate vascular dysfunction in the cerebral circulation and impaired neurovascular coupling of blood flow with metabolic demand, compared with controls (n=30); (2) to determine if Veterans with GWI (n=30) demonstrate autonomic dysregulation compared with controls (n=30); (3) to determine if impaired cerebrovascular and autonomic variables in Veterans with GWI are associated with neuroimaging biomarkers of cognitive decline.

Our first major task on the Statement of Work for this project was to obtain the necessary human subject approvals. This project has obtained local IRB approval, HRPO approval along with ClinicalTrials.gov registration. This first major task is 100% complete. Our next major task was training of trainees and students. Research staff has been trained on study specific protocols and on physiological measurements and radiology technicians have been trained on scanning protocols. This task is 100% complete. Our third major task was to initiate participant recruitment. Recruitment flyers and documents have been prepared and a list of organizations to contact for recruitment has been developed. This study has been open to recruitment since May 2022. We are preparing for research participant screenings and data collection. We have performed pilot MRI scans to test the MRI sequence to prepare for the MRI data collection. This task is 90% complete. Once we successfully complete data collection on the first participant, we will begin a large recruitment campaign, which will include posting flyers, social media announcements and contacting Veteran organizations in September 2022.

## **4. Impact**

This study received local IRB approval and HRPO approval in late February 2020. The University of Wisconsin-Madison shut down research laboratories and suspended all face-to-face human subject research in early March 2020. We received approval to restart human subjects research protocols on March 25, 2021. At this time we re-ordered and re-stocked supplies and had our equipment tested, calibrated and updated by the manufacturers. The space requirements within research laboratories were lifted in Fall 2021 allowing the laboratory to return to capacity and

perform re-training of the study protocol. Participant recruitment began in May 2022. Therefore, at this time, there are no results or significant impacts to report.

## **5. Changes/Problems**

Due to COVID-19-related disruptions, we were delayed in initiating recruitment and testing. In order to get approved to restart research, we now have additional requirements for safe research participant testing. This includes the need for additional PPE, air filters, and disposable supplies per participant study visit. In the past, we could sterilize and re-use equipment such as respiratory masks, but now we are required to move to single-use masks and tubing, which comes at a significant supply cost. In addition, there has been continued delays in obtaining supplies due to supply-chain interruptions. In May 2022, we opened the study to recruitment.

## **6. Products**

Nothing to Report.

## 7. Participants &amp; Other Collaborating Organizations

Name:	Jill Barnes, PhD
Project Role:	PI
Researcher Identifier:	0000-0001-6317-4153
Nearest person month worked:	Effort: 3 months Funding: 2 month
Contribution to Project:	Dr. Barnes has performed work in the area of obtaining local IRB approval, HRPO approval, equipment calibration, training of trainees and students, MRI protocol testing, and initiating recruitment.
Funding Support:	Funding for protected research time provided by the University of Wisconsin-Madison

Name:	Anna Howery, MS
Project Role:	Research Associate
Researcher Identifier:	
Nearest person month worked:	Effort: 3 months Funding: 3 months
Contribution to Project:	Ms. Howery has performed work in the area of obtaining local IRB approval, HRPO approval, revising study-specific protocols to comply with COVID-19-related regulations, performing equipment calibration and maintenance, ordering PPE and supplies, training of trainees and students, MRI protocol testing, assembling recruitment materials, and initiating recruitment.
Funding Support:	University of Wisconsin-Madison

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

The PI had a pending grant (NIH/NIA R03AG070469) awarded with 20% PI effort.

**What other organizations were involved as partners?**

Nothing to Report.

**8. Special Reporting Requirements**

None.

**9. Appendices**

None.