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14. ABSTRACT
The goal of this GWIRP project is to elucidate the mechanisms that subserve the brain function impairments in Gulf War Veterans' Illness with headache, with chronic headaches and body muscle and joint pain with and without comorbid depression through exploration of different features of brain function and connectivity whose impairment characterize widely prevalent chronic pain conditions. In pursuit of these goals, we acquired data from 15 healthy controls so far, and have analyzed 12 of them. We also analyzed the data of 50/51 GWVI-HAP veterans collected in the linked clinical trials so far.

15. SUBJECT TERMS
None listed.

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INTRODUCTION

An estimated 25% to 32% of 1991 Gulf War veterans experience multi-symptom conditions not explained by stress or psychiatric illness (1). Affecting up to 200,000 veterans deployed to Iraq, Kuwait, and Saudi Arabia during the 1991 Persian Gulf War, this poorly understood chronic medical condition referred to as Gulf War Illness (GWI), comprises a variety of behavioral and neurological symptoms and complaints including fatigue, generalized neuropathic pain, memory and concentration deficits, vestibular disturbances, and depression. Chronic pain is an especially common complaint in GWVI (2-5). Among the neurologic symptoms of brain impairment GWVI-related chronic headaches and body muscle and joint pain conditions (GWVI-HAP) are the most debilitating, affecting around 64% of the GWVI veterans (2, 6). Further, depression carries a very high co-morbid rate (>50%) in patients with chronic pain, including GWVI-HAP. These co-morbid pain and depressive symptoms are often associated with other neuropsychological dysfunction in attention, memory and systemic symptoms, which cast a profound negative impact on patients' quality of life (4, 7-10). The objective/goal of this project titled, “Exploring Mechanisms underlying Dysregulation of Central Nervous System in GWVI-HAP” is to discover the brain function mechanisms underlying GWVI-HAP with and without comorbid moderate/severe depression. This search for mechanisms of GWVI-HAP was to be accomplished by mapping the whole-brain functional connectivity (FC) network architecture of GWVI extracted from resting state functional magnetic resonance imaging (rsfMRI) data with different advanced techniques.

KEYWORDS: Gulf War Veterans Illness; GWVI-related chronic headaches and body muscle and joint pain; depression; mechanisms; resting state fMRI; functional connectivity; brain function networks advanced network analysis.

ACCOMPLISHMENTS

Major goals of the project in Quarters 1-8

According to the approved **Statement of Work** for the aims and goals for of this GWIRP project Exploring Brain Mechanisms Underlying Gulf War Illness through Advanced Network Analysis are (see also Table 1; which lists the Aims and Tasks by Quarter):

Specific Aim 1: To extract brain function mechanisms underlying GWVI-HAP by examining functional connectivity in different *a priori* postulated functional network models of chronic pain (Table 1).

Specific Aim 2: To comprehensively examine brain resting state fMRI networks with independent components analysis, in order to explore brain function mechanisms underlying GWVI-HAP

Specific Aim 3: To perform classification of the subjects into GWVI-HAPnodep, GWVI-HAPdep or HC based on unique features (i.e., *connectomics signatures)* of their functional connectome, and to elucidate brain mechanisms subserving GWVI-HAPnodep and GWVI-HAPdep, based on the *connectomics signatures*.

Specific Aim 4: To examine alterations in rsfMRI signal complexity across the brain

Table 1: ***Project Timelines:*** Project task schedules by quarter (Q) are tabulated below

Tasks	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Staff Recruitment	X							
fMRI Acquisition from HCs: Expected Complete			3	5	5	5	5	5
fMRI Acquisition from GWVI-HAP: Expected Complete	16*	8	8	8	8	8	8	8
rsfMRI Preprocessing		X	X	X	X	X	X	X
Specific Aim1		X	X	X	X	X	X	X
Specific Aim2		X	X	X	X	X	X	X
Specific Aim3		X	X	X	X	X	X	X
Specific Aim4		X	X	X	X	X	X	X

Dissemination of Results							X	X

Accomplishment of major goals

The tasks to be performed in this project till end of Quarter 8

Staff Recruitment: Staff Recruitment has been completed.

Acquisition of MRI data from GWVI-HAP veterans: Veterans with GWVI-HAP with and without comorbid depression are being conducted in a GWIRP Clinical trial GW180150 and VA CS R&D Merit Award (CX001986-01) both led by Dr Albert Leung. Dr. Anna Woodbury leads the Atlanta VAHCS arm of these trials. These two above-mentioned clinical trials are running behind schedule on subject recruitment. They have only collected 51 GWVI veterans' data until now. This is short of the target of 72 as per our Statement of Work. We have analyzed MRI data from 50/51 GWVI veterans.

Acquisition of MRI data from Healthy Controls: We were able to acquire and analyze 15 healthy control subjects. This is short of the target of 28 as per our Statement of Work. Initially, we had some difficulty recruiting subjects for this study, but this had been solved and we were able to obtain data from 5 healthy controls in just one month. Subsequently, our MRI system was dismantled and moved to a new state of art health science research building. However, due to unforeseen issues beyond our controls, such as delay in receiving permission from city and/or state authorities to occupy the new building, delay in receiving parts, etc. to bring our MRI scanner back online we could not resume our MRI scans till June 2023. Then we had another interruption due to transition in research coordinators. But it is heartening to note that we have 7 subjects in the last 5 weeks. Our new research coordinator has been very good at recruitment of volunteers. We are very optimistic that we will fulfill our recruitment goals.

Preprocessing and Parcellation of rsfMRI data: Resting state fMRI data from all subjects was preprocessed according to well-established pipelines (11, 12). The rsfMRI time-series were corrected for magnetic susceptibility induced image distortions, temporally shifted to account for differences in slice acquisition times, 3D volume registered to a base volume to account for global rigid motion; co-registered to the T1-weighted high-resolution anatomic scan using the well-established affine boundary based registration algorithm (13); spatially normalized to the MNI152 template; and resampled to 2mm X 2mm X 2mm voxel resolution. The spatially normalized time-series data were detrended of temporally and spatially structured artifacts caused by motion, draining veins, ventricular and white-matter specific signals, susceptibility artifacts, and physiological noise with the sophisticated ICA-based FIX technique (14). The resultant time-series were detrended of low frequency drifts (with a 0.01 Hz cutoff high-pass filter), as well as well as the six rigid-body motion parameters, as well as deep cerebral white matter signals, and spatially smoothed with an isotropic Gaussian filter (FWHM = 5 mm). The pre-processed fMRI time-series were parcellated based on the well-established 274-ROI Brainnetome atlas (15), for Specific Aim 3. We were able to complete this task on the 50/51 GWVIs and 12/15 Healthy Controls collected so far.

Performing Seed Based Functional Connectivity Analysis (SA 1): Instead of performed seed-based cross-correlation analysis (SB-CCA) employing just a few selected ROIs as proposed, we obtained Brainnetome ROI connectivity matrices yielding information about FC between all 274 Brainnetome ROIs. This in effect expanded the scope of SA1, to performing both exploratory as well as hypothesis-based SB-CCA. We were able to complete this task 50/51 GWVIs and 12/15 Healthy Controls collected so far. We fed a subset of this data that were relatively artifact free to a support vector machine classifier which yielded interesting results (see SA3 below).

Performing Group ICA Based Analysis of Resting State Networks (SA2):

The pre-processing (as described above) for conducting Group ICA (GICA) has been completed on the 50/51 GWVIs and 12/15 Healthy Controls collected so far. GICA requires an adequate sample size in all three groups to provide meaningful reproducible results, which we do expect to possess soon.

SVM-based Classification of subjects (SA3):

The pre-processing (as described above) for conducting support vector machine (SVM)-based classification has been completed on the 50/51 GWVIs and 12/15 Healthy Controls collected so far. Multiclass ordinal SVM classification requires an adequate sample size in all three groups to provide meaningful reproducible results, which we do not yet possess among HCs. However, we were able to perform binary GWInodep vs GWIdep SVM classification on a subset of subject Brainnetome FC matrices obtained from data that were relatively artifact free. This classifier was able to predict the health status of GWI veterans with close to 90% accuracy (obtained through cross-validation). The SVM classifier yields importance scores too all connections in Brainnetome connectome based on their contribution to the classifier used to distinguish the two groups. The Table below shows the results of the classification.

Right Prefrontal Thalamu[1]	
GWInodep < GWIdep	Sensorimotor regions (somatosensory cortices, motor cortex, supplementary motor area, paracentral lobule, intraparietal areas, mid cingulate), cortico-limbic network regions (ventromedial prefrontal cortex, subgenual cingulate, posterior orbitofrontal complex, amygdala, hippocampus, Brodmann area 38, anterior temporal lobe), default mode network, superior temporal gyrus
Right Inferior Frontal Junction[2]	
GWInodep < GWIdep	Parietal premotor network, Sensorimotor regions, auditory cortex
GWInodep > GWIdep	Executive functions areas: medial dorsal thalamus, basal ganglia, cerebellar crus I and crus II
Left Ventrolateral Anterior Insula	
GWInodep < GWIdep	Limbic areas (subgenual cingulate, posterior orbitofrontal complex, anterior medial temporal lobe, amygdala), insula, cingulate, visual cortex, fusiform gyrus, pulvinar
Right Sensory Thalamus[3]	
GWInodep < GWIdep	Sensory and parietal association areas: Insula, auditory cortex, superior temporal gurus, dorsal anterior cingulate, superior parietal lobe, intraparietal sulcus, primary somatosensory cortex, occipitotemporal cortex, fusiform face area, visual cortex
GWInodep > GWIdep	Parietal association areas: cerebellar crus I and crus II
Left Subgenual Cingulate and Posterior Orbitofrontal Complex	
GWInodep < GWIdep	Ventrolateral, dorsolateral, and dorsomedial prefrontal, inferior and medial frontal cortices, anterior cingulate, anterior superior, middle and inferior temporal gyri, precuneus, lateral parietal cortex, nucleus accumbens, thalamus.
Right Entorhinal Cortex	
GWInodep < GWIdep	Sensorimotor areas, auditory cortex, insula, putamen, amygdala, medial temporal lobe
GWInodep > GWIdep	Inferior temporal visual association region
Left Nucleus Accumbens	
GWInodep < GWIdep	Limbic areas: (ventromedial prefrontal cortex, subgenual cingulate, posterior orbitofrontal cortex, anterior superior temporal gyrus, amygdala, hippocampus), medial temporal lobe, fusiform face and visual word form areas, parieto-occipital cortex, sensorimotor areas, auditory cortex, vestibular cortex
Left Brodmann Area 39c[4]	
GWInodep < GWIdep	Superior parietal lobule, intraparietal sulcus, parieto-occipital cortex, occipitotemporal cortex, fusiform, insula, anterior cingulate, ventral posterolateral thalamus
GWInodep > GWIdep	Left Inferior Frontal Sulcus
Left Cerebellum Crus I	

GWInodep > GWIdep	Dorsolateral prefrontal and inferior frontal cortices, premotor cortex, Broca's Area, thalamus, parieto-occipital cortex, visual cortex, occipitotemporal cortex

[1] Prefrontal thalamus contains parts of ventral anterior, ventral lateral, ventral posterior lateral, intralaminar, medial dorsal and lateral dorsal, and pulvinar thalamic nuclei
[2] Inferior frontal junction ROI encompasses some of premotor and inferior frontal cortices
[3] Somatosensory thalamus contains ventral posterior medial, ventral posterior lateral nuclei, and parts of medial geniculate and pulvinar nuclei
4 Brodmann Area 39C brainnetome node includes parts of BA39, temporoparietal occipital junction, and intraparietal areas

These results indicate that GWI-HAP subjects without depression exhibit diminished FC with brain function networks connected to the ROIs listed above. On the other hand, GWI-HAP subjects with depression group exhibited hyperconnectivity (except cognitive prefrontal cortex) especially in limbic regions and somatosensory and sensory-associative areas involved in perception of pain. These results are consistent with prior depression and pain studies. Hyperconnectivity across the brain in concert with hypoconnectivity of prefrontal cortex, putatively linked to NMDA receptor hypofunction has been observed in chronic depression (16). Enhanced activity in somatosensory, and sensory association areas have been observed in GWI (12, 17), as well as other disease models of chronic pain (18)..

Performing Multi-Scale Entropy Analysis (SA4):

We have completed the multi-scale entropy-based fMRI complexity analysis on the 40 GWVI and 5 HC datasets collected so far. Sample entropy (SE) was calculated at 10 temporal scales to obtain multi-scale entropy (MSE). The window-length *m* for SE calculations was set to 2, and the distance threshold *r* set to 0.3 based on well-established methods (19, 20). ROI-averaged MSE was also obtained from the 274 Brainnetome ROIs.

Significant results or key outcomes: Nothing to Report.

Other Achievements: We were invited to present our preliminary findings of this project in a oral abstract presentation at the International Neuropsychological Society meeting in San Diego in February 2023.

Opportunities for training and professional development: Not applicable to this grant

IMPACT

Impact on the development of the principal discipline(s) of the project: Nothing to report.

Impact on other disciplines: Nothing to report.

Impact on technology transfer: Nothing to report.

Impact on society beyond science and technology: Nothing to report.

CHANGES/PROBLEMS

Recruitment of GWVI veterans in the clinical trials whose data this project depends on has been behind schedule. Hence, we were not able to meet our target of datasets to analyze. Recruitment of human control subjects in the age-group needed for this project was a bit challenging. However, we have found more success in attracting volunteers after we very recently put an advertisement in a newspaper targeting seniors and were able to acquire data from 5 subjects withing a month. However, we experienced a delay due to the time it took to obtain a certificate of occupancy from the city of Atlanta for new research building where our MRI facilities have been shifted to. We are confident of meeting our goals for the next reporting period.

This is short of the target of 28 as per our Statement of Work. Initially, we had some difficulty recruiting subjects for this study, but this had been solved after we started to advertise for more volunteers. Subsequently, our MRI system was dismantled and moved to a new state of art health

science research building. However, due to unforeseen issues beyond our controls, such as delay in receiving permission from city and/or state authorities to occupy the new building, delay in receiving parts, etc. to bring our MRI scanner back online we could not resume our MRI scans till June 2023. Then we had another interruption due to transition in research coordinators. But it is heartening to note that we have 7 subjects in the last 5 weeks. Our new research coordinator has been very good at recruitment of volunteers. We are very optimistic that we will fulfill our recruitment goals.

PRODUCTS

We presented an abstract based on our preliminary findings at the International Neuropsychological Society meeting in San Diego in February 2023.

More comprehensive dissemination of Results is not scheduled to occur till Year 2.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Emory University Personnel

Name	**Kaundinya Gopinath, PhD.**
Project Role	Principal Investigator (PI) of the DoD CDMRP GWIRP award
Research Identifier	ERA Commons: KGOPIN
Nearest person month worked:	2.64 calendar months
Contribution to Project:	Dr. Gopinath took part in all the tasks completed. He supervised all work on the project. He shared data analysis responsibilities with the Graduate Research Assistant Gabriell Champion. He also designed data analysis methodology adopted in the project. In this he received constructive input from the co-investigators (co-Is) Drs Ying Guo, Keith McGregor and Albert Leung. He shared administrative tasks pertaining to IRB-related matters with the

	graduate student Gabriell Champion, and after Ms Champion's departure our new research coordinator Sara Yang Kim.

Name	**Ying Guo, PhD.**
Project Role	Co-Investigator
Research Identifier	ERA Commons: YGUO76
Nearest person month worked:	1.2 calendar months
Contribution to Project:	Dr. Guo provided constructive input into design and execution of data analysis methodology adopted in the project. She also supervised a graduate student funded by our grant, Guangming Yang who was instrumental in SVM classification.

Other collaborating Organization 1:

Organization 1 Name: Veterans Medical Research Foundation (VMRF)

Location of Organization 1: Address: 3350 La Jolla Village Dr. (151A), San Diego, Ca. 92161

Partner's contribution to the project: Collaboration through Emory-VMRF sub-contract under the DoD GWIRP award for this project

VMRF Sub-Contract Personnel

Name	**Albert Leung, MD.**
Project Role	Co-Investigator
Research Identifier	ERA Commons: AYLEUNG
Nearest person month worked:	1.2 calendar months
Contribution to Project:	Dr. Leung is the main PI of the clinical trials whose data is being examined in this project. He provided constructive input into design of project methodology based on his expertise in the field of GWVI rehabilitation therapy.

Other collaborating Organization 2:

Organization 2 Name: Department of Psychology, Georgia State University

Location of Organization 2: Address: 140 Decatur St SE, Atlanta, GA 30303

Partner's contribution to the project: Collaboration through Emory-GSU sub-contract under the DOD GWIRO award for this project

GSU Sub-Contract Personnel

Name	**Gabriell Champion, BS.**
Project Role	Graduate Student
Research Identifier	
Nearest person month worked:	1.2 calendar months
Contribution to Project:	Ms. Champion shared data analysis responsibilities under the supervision of Dr. Gopinath. She also performed administrative research coordination tasks including creating IRB documentation under Dr. Gopinath's guidance. Ms. Champion left for an opportunity with her PhD advisor at her parent institution. This sub-contracted ended in June 2023.

Other collaborating Organization 3:

Organization 3 Name: Center for Visual and Neurocognitive Rehabilitation, Atlanta VAHCS

Location of Organization 3: Address: 1670, Clairmont Road, Decatur, GA 30033

Partner's contribution to the project: Collaboration through Emory- Atlanta VAHCS Sub-Contract

Name	**Keith McGregor, PhD.**
Project Role	Co-Investigator
Research Identifier	ERA Commons: KMCGREGOR

Nearest person month worked:	1.2 calendar months (in-kind; no salary support)
Contribution to Project:	Dr McGregor provided constructive input into design of project methodology based on his expertise in cognitive neuroscience. Dr McGregor has shifted to another university, but he still maintains courtesy appointment in Atlanta VAHCS and is able to continue participating in the project without beak

APPENDIX 1: REFERENCES

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