

**Research Advisory Committee on  
Gulf War Veterans' Illnesses (RACGWVI)  
— PubMed Research Citations  
for April, May, June 2022**

Prepared by Staff of the RACGWVI.

## **RACGWVI: Gulf War Illness — PubMed Citations for April, May, June 2022**

The following is a list of published research projects that focus on Gulf War Illness (GWI) for the months of April, May and June 2022.

For further VA research updates please visit, VA RESEARCH CURRENTS — Research News from the U.S. Department of Veterans Affairs. [VA Research Currents - Home](#)

### **Hyperlinks Guide:**

**Table of Contents:** Each title in the table of contents is linked to that corresponding abstract. Click on the desired title to go to that page (e.g., Health-Related Quality of Life by Gulf War Illness Case Status, page 2).

**Article Title:** The title on each page (excluding table of contents), links to the abstract at PubMed.

**DOI:** Selecting the digital object identifier (DOI) will link to the article publication website.

**Table of Contents**

Oral Nano-Curcumin in a Model of Chronic Gulf War Illness Alleviates Brain Dysfunction with Modulation of Oxidative Stress, Mitochondrial Function, Neuroinflammation, Neurogenesis, and Gene Expression..... 1

Health-Related Quality of Life by Gulf War Illness Case Status.....2

Comparing psychosocial functioning, suicide risk, and nonsuicidal self-injury between veterans with probable posttraumatic stress disorder and alcohol use disorder .....3

Management of Chronic Multisymptom Illness: Synopsis of the 2021 US Department of Veterans Affairs and US Department of Defense Clinical Practice Guideline.....4

Neurogenesis and chronic neurobehavioral outcomes are partially improved by vagus nerve stimulation in a mouse model of Gulf War illness.....5

Pyridostigmine bromide elicits progressive and chronic impairments in the cholinergic anti-inflammatory pathway in the prefrontal cortex and hippocampus of male rats.....6

Million Veteran Program's response to COVID-19: Survey development and preliminary findings.... 7

Therapeutic role of curcumin in adult neurogenesis for management of psychiatric and neurological disorders: a scientometric study to an in-depth review.....9

Brain-Specific Increase in Leukotriene Signaling Accompanies Chronic Neuroinflammation and Cognitive Impairment in a Model of Gulf War Illness..... 10

Neuroimmune signatures in chronic low back pain subtypes..... 11

Dry Eye Symptoms and Signs in US Veterans With Gulf War Illness ..... 12

Invited Perspective: Causal Implications of Gene by Environment Studies Applied to Gulf War Illness ..... 13

Evaluation of a Gene-Environment Interaction of PON1 and Low-Level Nerve Agent Exposure with Gulf War Illness: A Prevalence Case-Control Study Drawn from the U.S. Military Health Survey's National Population Sample..... 14

Regulatory Modulations and Dendritic Arborization in the Mouse Hippocampus Following Gulf War Toxicant Exposure..... 15

Utility of the ALSFRS-R for predicting ALS and comorbid disease neuropathology: The Veterans Affairs Biorepository Brain Bank..... 16

Comment on "Evaluation of a Gene-Environment Interaction of PON1 and Low-Level Nerve Agent Exposure with Gulf War Illness: A Prevalence Case-Control Study Drawn from the U.S. Military Health Survey's National Population Sample"..... 17

Response to "Comment on 'Evaluation of a Gene-Environment Interaction of PON1 and Low-Level Nerve Agent Exposure with Gulf War Illness: A Prevalence Case-Control Study Drawn from the U.S. Military Health Survey's National Population Sample'" ..... 18

Response to "Comment on 'Evaluation of a Gene-Environment Interaction of PON1 and Low-Level Nerve Agent Exposure with Gulf War Illness: A Prevalence Case-Control Study Drawn from the U.S. Military Health Survey's National Population Sample'" ..... 19

Host gut resistome in Gulf War chronic multisymptom illness correlates with persistent inflammation .....20

Pain, but not Physical Activity, is Associated with Gray Matter Volume Differences in Gulf War Veterans with Chronic Pain.....21

**RACGWI: Gulf War Illness — PubMed Citations for April, May, June 2022**

Nutrient Intake as a Predictor of Health Improvement on the Low Glutamate Diet in Veterans With Gulf War Illness (GWI).....22

**Oral Nano-Curcumin in a Model of Chronic Gulf War Illness Alleviates Brain Dysfunction with Modulation of Oxidative Stress, Mitochondrial Function, Neuroinflammation, Neurogenesis, and Gene Expression**

Aging Dis. 2022 Apr 1;13(2):583-613. doi: [10.14336/AD.2021.0829](https://doi.org/10.14336/AD.2021.0829). eCollection 2022 Apr.

Sahithi Attaluri 1, Meenakshi Arora 2, Leelavathi N Madhu 1, Maheedhar Kodali 1, Bing Shuai 1, Laila Melissari 1, Raghavendra Upadhyya 1, Xiaolan Rao 1, Adrian Bates 1, Eeshika Mitra 1, Keyhan R Ghahfarouki 1, M N V Ravikumar 2, Ashok K Shetty 1

**Affiliations**

11Institute for Regenerative Medicine, Department of Molecular and Cellular Medicine, Texas A&M University College of Medicine, College Station, Texas, USA.

22Department of Pharmaceutical Sciences, Irma Lerma Rangel College of Pharmacy, Texas A&M University, College Station, Texas, USA.

**Abstract**

Unrelenting cognitive and mood impairments concomitant with incessant oxidative stress and neuroinflammation are among the significant symptoms of chronic Gulf War Illness (GWI). Curcumin (CUR), an antiinflammatory compound, has shown promise to alleviate brain dysfunction in a model of GWI following intraperitoneal administrations at a high dose. However, low bioavailability after oral treatment has hampered its clinical translation. Therefore, this study investigated the efficacy of low-dose, intermittent, oral polymer nanoparticle encapsulated CUR (nCUR) for improving brain function in a rat model of chronic GWI. Intermittent administration of 10 or 20 mg/Kg nCUR for 8 weeks in the early phase of GWI improved brain function and reduced oxidative stress (OS) and neuroinflammation. We next examined the efficacy of 12-weeks of intermittent nCUR at 10 mg/Kg in GWI animals, with treatment commencing 8 months after exposure to GWI-related chemicals and stress, mimicking treatment for the persistent cognitive and mood dysfunction displayed by veterans with GWI. GWI rats receiving nCUR exhibited better cognitive and mood function associated with improved mitochondrial function and diminished neuroinflammation in the hippocampus. Improved mitochondrial function was evident from normalized expression of OS markers, antioxidants, and mitochondrial electron transport genes, and complex proteins. Lessened neuroinflammation was noticeable from reductions in astrocyte hypertrophy, NF- $\kappa$ B, activated microglia with NLRP3 inflammasomes, and multiple proinflammatory cytokines. Moreover, nCUR treated animals displayed enhanced neurogenesis with a normalized expression of synaptophysin puncta, and multiple genes linked to cognitive dysfunction. Thus, low-dose, intermittent, oral nCUR therapy has promise for improving brain function in veterans with GWI.

## **Health-Related Quality of Life by Gulf War Illness Case Status**

Int J Environ Res Public Health. 2022 Apr 7;19(8):4425. doi: [10.3390/ijerph19084425](https://doi.org/10.3390/ijerph19084425).

Elizabeth J Gifford 1 2, Stephen H Boyle 1, Jacqueline Vahey 1 3, Kellie J Sims 1, Jimmy T Efird 1 4, Blair Chesnut 1, Crystal Stafford 1, Julie Upchurch 1, Christina D Williams 1, Drew A Helmer 5 6, Elizabeth R Hauser 1 7

### **Affiliations**

1Cooperative Studies Program Epidemiology Center-Durham, Durham VA Medical Center, Durham VA Health Care System, Durham, NC 27705, USA.

2Center for Child and Family Policy, Duke Margolis Center for Health Policy, Duke University Sanford School of Public Policy, Durham, NC 27708, USA.

3Computational Biology and Bioinformatics Program, Duke University School of Medicine, Durham, NC 27705, USA.

4Department of Radiation Oncology, School of Medicine, Case Western Reserve University, Cleveland, OH 44106, USA.

5Center for Innovations in Quality, Effectiveness and Safety (IQuEST), Michael E. DeBakey VA Medical Center, Houston, TX 77030, USA.

6Department of Medicine, Baylor College of Medicine, Houston, TX 77030, USA.

7Department of Biostatistics and Bioinformatics, Duke University Medical Center, Duke Molecular Physiology Institute, Durham, NC 27710, USA.

### **Abstract**

This study examines how health-related quality of life (HRQOL) and related indices vary by Gulf War illness (GWI) case status. The study population included veterans from the Gulf War Era Cohort and Biorepository (n = 1116). Outcomes were physical and mental health from the Veterans RAND 12 and depression, post-traumatic stress (PTSD), sleep disturbance, and pain. Kansas (KS) and Centers for Disease Control and Prevention (CDC) GWI definitions were used. Kansas GWI derived subtypes included GWI (met symptom criteria; no exclusionary conditions (KS GWI: Sym+/Dx-)) and those without GWI: KS noncase (1): Sym+/Dx+, KS noncase (2): Sym-/Dx+, and noncase (3): Sym-/Dx-. CDC-derived subtypes included CDC GWI severe, CDC GWI mild-to-moderate and CDC noncases. Case status and outcomes were examined using multivariable regression adjusted for sociodemographic and military-related characteristics. Logistic regression analysis was used to examine associations between GWI case status and binary measures for depression, PTSD, and severe pain. The KS GWI: Sym+/Dx- and KS noncase (1): Sym+/Dx+ groups had worse mental and physical HRQOL outcomes than veterans in the KS noncase (2): Sym-/Dx+ and KS noncase (3): Sym-/Dx- groups (ps < 0.001). Individuals who met the CDC GWI severe criteria had worse mental and physical HRQOL outcomes than those meeting the CDC GWI mild-to-moderate or CDC noncases (ps < 0.001). For other outcomes, results followed a similar pattern. Relative to the less symptomatic comparison subtypes, veterans who met the Kansas symptom criteria, regardless of exclusionary conditions, and those who met the CDC GWI severe criteria experienced lower HRQOL and higher rates of depression, PTSD, and severe pain.

**Comparing psychosocial functioning, suicide risk, and nonsuicidal self-injury between veterans with probable posttraumatic stress disorder and alcohol use disorder**

J Affect Disord. 2022 Apr 7; 308:10-18. doi: [10.1016/j.jad.2022.04.006](https://doi.org/10.1016/j.jad.2022.04.006). Online ahead of print.

Shannon M Blakey 1, Sarah C Griffin 2, Jeremy L Grove 3, Samuel C Peter 4, Ryan D Levi 4, Patrick S Calhoun 5, Eric B Elbogen 6, Jean C Beckham 5, Mary J Pugh 7, Nathan A Kimbrel 5

**Affiliations**

1Durham VA Health Care System, Durham, NC, United States of America; VA Mid-Atlantic Mental Illness Research, Education and Clinical Center, Durham, NC, United States of America; RTI International, Research Triangle Park, NC, United States of America. Electronic address: Shannon.Blakey@duke.edu.

2Durham VA Health Care System, Durham, NC, United States of America; VA Mid-Atlantic Mental Illness Research, Education and Clinical Center, Durham, NC, United States of America.

3Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine, Durham, NC, United States of America.

4Durham VA Health Care System, Durham, NC, United States of America.

5Durham VA Health Care System, Durham, NC, United States of America; VA Mid-Atlantic Mental Illness Research, Education and Clinical Center, Durham, NC, United States of America; Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine, Durham, NC, United States of America.

6VA Mid-Atlantic Mental Illness Research, Education and Clinical Center, Durham, NC, United States of America; Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine, Durham, NC, United States of America; VA National Center on Homelessness Among Veterans, Tampa, FL, United States of America.

7VA Salt Lake City Healthcare System, Salt Lake City, UT, United States of America; University of Utah School of Medicine, Salt Lake City, UT, United States of America.

**Abstract**

**Background:** Posttraumatic stress disorder (PTSD) and alcohol use disorder (AUD) are each common among United States (U.S.) military veterans and frequently co-occur (i.e., PTSD+AUD). Although comorbid PTSD+AUD is generally associated with worse outcomes relative to either diagnosis alone, some studies suggest the added burden of comorbid PTSD+AUD is greater relative to AUD-alone than to PTSD-alone. Furthermore, nonsuicidal self-injury (NSSI) is more common among veterans than previously thought but rarely measured as a veteran psychiatric health outcome. This study sought to replicate and extend previous work by comparing psychosocial functioning, suicide risk, and NSSI among veterans screening positive for PTSD, AUD, comorbid PTSD+AUD, and neither disorder.

**Methods:** This study analyzed data from a national sample of N = 1046 U.S. veterans who had served during the Gulf War. Participants self-reported sociodemographic, functioning, and clinical information through a mailed survey.

**Results:** Veterans with probable PTSD+AUD reported worse psychosocial functioning across multiple domains compared to veterans with probable AUD, but only worse functioning related to controlling violent behavior when compared to veterans with probable PTSD. Veterans with probable PTSD+AUD reported greater suicidal ideation and NSSI than veterans with probable AUD, but fewer prior suicide attempts than veterans with probable PTSD.

**Limitations:** This study was cross-sectional, relied on self-report, did not verify clinical diagnoses, and may not generalize to veterans of other military conflicts.

**Conclusions:** Findings underscore the adverse psychiatric and functional outcomes associated with PTSD and comorbid PTSD+AUD, such as NSSI, and highlight the importance of delivering evidence-based treatment to this veteran population.

**Management of Chronic Multisymptom Illness: Synopsis of the 2021 US Department of Veterans Affairs and US Department of Defense Clinical Practice Guideline**

Mayo Clin Proc. 2022 Apr 9;S0025-6196(22)00065-9. doi: [10.1016/j.mayocp.2022.01.031](https://doi.org/10.1016/j.mayocp.2022.01.031). Online ahead of print.

Rachel Robbins 1, Drew Helmer 2, Patrick Monahan 3, Stephen Hunt 4, Lisa McAndrew 5, Mitchell Nazario 6, William J Brown 7, Wendy Chao 8, Aniceto Navarro 9, James Sall 10

**Affiliations**

1Associate Program Director, Rheumatology Fellowship, Walter Reed National Military Medical Center, Bethesda, MD.

2Deputy Director, Center for Innovations in Quality, Effectiveness and Safety, Michael E. DeBakey VA Medical Center, Houston, TX.

3Director, Integrated Clinical Skills, Uniformed Services University of the Health Sciences, Bethesda, MD.

4VA National Director Post-Deployment Integrated Care Initiative, VA Puget Sound Health Care System, Seattle, WA.

5Acting Director of Research, War Related Illness and Injury Study Center, VA New Jersey Health Care System, East Orange, NJ.

6National PBM Clinical Program Manager for Pain and Substance Abuse, Veterans Health Administration, Hines, IL.

7Chief, Center for Nursing Science and Clinical Inquiry, Landstuhl Regional Medical Center, Germany.

8Chief, Neurology Services, San Antonio Military Medical Center, Fort Sam Houston, TX.

9Consultation Liaison Psychiatry/Geriatric Psychiatry, Fort Belvoir Community Hospital, Fort Belvoir, VA.

10Clinical Quality Specialist, Office of Evidence-Based Practice, VA Central Office, Washington, DC.  
Electronic address: [james.sall@va.gov](mailto:james.sall@va.gov).

**Abstract**

In 2019, senior leaders within the US Department of Veterans Affairs and the US Department of Defense commissioned the update of a clinical practice guideline for managing chronic multisymptom illness. Clinical experts were assembled across both agencies to systematically review evidence and to develop treatment recommendations based on that evidence. This effort resulted in the development of 29 evidence-based recommendations for providing care for individuals with chronic multisymptom illness.



**Neurogenesis and chronic neurobehavioral outcomes are partially improved by vagus nerve stimulation in a mouse model of Gulf War illness**

Neurotoxicology. 2022 Apr 11; 90:205-215. doi: [10.1016/j.neuro.2022.04.001](https://doi.org/10.1016/j.neuro.2022.04.001). Online ahead of print.

Jaclyn Iannucci 1, Damir Nizamutdinov 2, Lee A Shapiro 3

**Affiliations**

1Texas A&M University College of Medicine, USA.

2Baylor Scott and White Health, USA.

3Texas A&M University College of Medicine, USA. Electronic address: [lshapiro@tamu.edu](mailto:lshapiro@tamu.edu).

**Abstract**

Gulf War illness (GWI) is a chronic, multi-symptom disorder that has impacted approximately one third of Gulf War veterans. GWI and its symptoms have been linked to the exposure to neurological chemicals, including the anti-nerve gas drug pyridostigmine bromide (PB) and the insecticide permethrin (PER), among others. Mouse models utilizing these chemicals have reported symptomology analogous to human GWI. These changes include behavioral and cognitive impairment, neuroinflammation and hippocampal pathogenesis. Disease modifying interventions that target these pathological components are desperately needed. Vagus nerve stimulation (VNS) is FDA approved for drug-resistant epilepsy and depression. VNS has also been used off-label to target a myriad of symptoms, some of which are encompassed within the Kansas and CDC definitions of clinical GWI symptomology. A GWI animal model in which mice are exposed to a daily injection of PB and PER for 10 consecutive days has been shown to exhibit cognitive impairment and hippocampal pathology. The purpose of this study was to determine if 2-4 weeks of continuous vagus nerve stimulation initiated at 32 weeks after exposure to PB and PER would improve cognitive performance and hippocampal pathology. The results of the study revealed that exposure to PB and PER produces long-term cognitive deficits and reduced hippocampal neurogenesis. The results also showed that the VNS treatment was anxiolytic, improved some aspects of pattern separation deficits, and mitigated the reduced hippocampal neurogenesis. Thus, VNS improves outcomes in a mouse model of GWI and should be examined as a potential therapeutic strategy for mitigating some symptomology associated with GWI.

**Pyridostigmine bromide elicits progressive and chronic impairments in the cholinergic anti-inflammatory pathway in the prefrontal cortex and hippocampus of male rats**

Neurobiol Stress. 2022 Apr 15; 18:100446. doi: [10.1016/j.ynstr.2022.100446](https://doi.org/10.1016/j.ynstr.2022.100446). eCollection 2022 May.

H E Burzynski 1, V A Macht 1, J L Woodruff 1, J N Crawford 1, J M Erichsen 1, G G Piroli 1, C A Grillo 1 2, J R Fadel 1 2, L P Reagan 1 2

**Affiliations**

1University of South Carolina School of Medicine, Department of Pharmacology, Physiology, and Neuroscience, Columbia, SC, 29208, USA.

2Columbia VA Health Care System, Columbia, SC, 29208, USA.

**Abstract**

Gulf War Illness (GWI) is a multi-symptom illness that continues to affect over 250,000 American Gulf War veterans. The causes of GWI remain equivocal; however, prophylactic use of the acetylcholinesterase inhibitor pyridostigmine bromide (PB), and the stress of combat have been identified as two potential causative factors. Both PB and stress alter acetylcholine (ACh), which mediates both cognition and anti-inflammatory responses. As inflammation has been proposed to contribute to the cognitive deficits and immune dysregulation in GWI, the goal of this study was to determine the long-term effects of PB and stress on the cholinergic anti-inflammatory pathway in the central nervous system and periphery. We used our previously established rat model of GWI and in vivo microdialysis to assess cholinergic neurochemistry in the prefrontal cortex (PFC) and hippocampus following a mild immune challenge (lipopolysaccharide; LPS). We then examined LPS-induced changes in inflammatory markers in PFC and hippocampal homogenates. We found that PB treatment produces a long-lasting potentiation of the cholinergic response to LPS in both the PFC and hippocampus. Interestingly, this prolonged effect of PB treatment enhancing cholinergic responses to LPS was accompanied by paradoxical increases in the release of pro-inflammatory cytokines in these brain regions. Collectively, these findings provide evidence that neuroinflammation resulting from dysregulation of the cholinergic anti-inflammatory pathway is a mechanistic mediator of the progression of the neurochemical and neurocognitive deficits in GWI and more broadly suggest that dysregulation of this pathway may contribute to neuroinflammatory processes in stress-related neurological disorders.

## Million Veteran Program's response to COVID-19: Survey development and preliminary findings

PLoS One. 2022 Apr 25;17(4):e0266381. doi: [10.1371/journal.pone.0266381](https://doi.org/10.1371/journal.pone.0266381). eCollection 2022.

Stacey B Whitbourne 1 2 3, Xuan-Mai T Nguyen 1 4, Rebecca J Song 1 5, Emily Lord 1, Michelle Lyden 1, Kelly M Harrington 1 6, Rachel Ward 1 7 8, Yanping Li 1, Jessica V V Brewer 1, Kelly M Cho 1 2 3, Luc Djousse 1 2 3 7, Sumitra Muralidhar 9, Philip S Tsao 10 11 12, J Michael Gaziano 1 2 3, Juan P Casas 1 2 3, MVP COVID-19 Science Program

### Affiliations

1Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), VA Boston Healthcare System, Boston, MA, United States of America.

2Department of Medicine, Harvard Medical School, Boston, MA, United States of America.

3Division of Aging, Department of Medicine, Brigham and Women's Hospital, Boston, MA, United States of America.

4Carle Illinois College of Medicine, University of Illinois, Champaign, IL, United States of America.

5Department of Epidemiology, Boston University School of Public Health, Boston, MA, United States of America.

6Department of Psychiatry, Boston University School of Medicine, Boston, MA, United States of America.

7New England Geriatric Research, Education, and Clinical Center (GRECC), VA Boston Healthcare System, Boston, MA, United States of America.

8Department of Physical Medicine and Rehabilitation, Harvard Medical School, Boston, MA, United States of America.

9Office of Research and Development, Veterans Health Administration, Washington, D.C., United States of America.

10VA Palo Alto Epidemiology Research and Information Center for Genomics, VA Palo Alto Health Care System, Palo Alto, CA, United States of America.

11Department of Medicine, Stanford University School of Medicine, Stanford, CA, United States of America.

12Stanford Cardiovascular Institute, Stanford University School of Medicine, Stanford, CA, United States of America.

### Abstract

**Background:** In response to the novel Coronavirus Disease 2019 (COVID-19) pandemic, the Department of Veterans Affairs (VA) Million Veteran Program (MVP) organized efforts to better understand the impact of COVID-19 on Veterans by developing and deploying a self-reported survey.

**Methods:** The MVP COVID-19 Survey was developed to collect COVID-19 specific elements including symptoms, diagnosis, hospitalization, behavioral and psychosocial factors and to augment existing MVP data with longitudinal collection of key domains in physical and mental health. Due to the rapidly evolving nature of the pandemic, a multipronged strategy was implemented to widely disseminate the COVID-19 Survey and capture data using both the online platform and mailings.

**Results:** We limited the findings of this paper to the initial phase of survey dissemination which began in May 2020. A total of 729,625 eligible MVP Veterans were invited to complete version 1 of the COVID-19 Survey. As of October 31, 2020, 58,159 surveys have been returned. The mean and standard deviation (SD) age of responders was 71 (11) years, 8.6% were female, 8.2% were Black, 5.6% were Hispanic, and 446 (0.8%) self-reported a COVID-19 diagnosis. Over 90% of responders reported wearing masks, practicing social distancing, and frequent hand washing.

## **RACGWVI: Gulf War Illness — PubMed Citations for April, May, June 2022**

**Conclusion:** The MVP COVID-19 Survey provides a systematic collection of data regarding COVID-19 behaviors among Veterans and represents one of the first large-scale, national surveillance efforts of COVID-19 in the Veteran population. Continued work will examine the overall response to the survey with comparison to available VA health record data.

**Therapeutic role of curcumin in adult neurogenesis for management of psychiatric and neurological disorders: a scientometric study to an in-depth review**

Crit Rev Food Sci Nutr. 2022 Apr 28;1-13. doi: [10.1080/10408398.2022.2067827](https://doi.org/10.1080/10408398.2022.2067827). Online ahead of print.

Wenxin Ma 1, Dong Xu 1, Lucy Zhao 2, Mengmeng Yuan 1, Yuan-Lu Cui 1, Yue Li 1

**Affiliations**

1State Key Laboratory of Component-Based Chinese Medicine, Ministry of Education Key Laboratory of Pharmacology of Traditional Chinese Medicine Formulae, Institute of Traditional Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin, China.

2Wolfson Centre for Age-Related Diseases, King's College London, London, UK.

**Abstract**

Aberrant neurogenesis is a major factor in psychiatric and neurological disorders that have significantly attracted the attention of neuroscientists. Curcumin is a primary constituent of curcuminoid that exerts several positive pharmacological effects on aberrant neurogenesis. First, it is important to understand the different processes of neurogenesis, and whether their dysfunction promotes etiology as well as the development of many psychiatric and neurological disorders; then investigate mechanisms by which curcumin affects neurogenesis as an active participant in pathophysiological events. Based on scientometric studies and additional extensive research, we explore the mechanisms by which curcumin regulates adult neurogenesis and in turn affects psychiatric diseases, i.e., depression and neurological disorders among them traumatic brain injury (TBI), stroke, Alzheimer's disease (AD), Gulf War Illness (GWI) and Fragile X syndrome (FXS). This review aims to elucidate the therapeutic effects and mechanisms of curcumin on adult neurogenesis in various psychiatric and neurological disorders. Specifically, we discuss the regulatory role of curcumin in different activities of neural stem cells (NSCs), including proliferation, differentiation, and migration of NSCs. This is geared toward providing novel application prospects of curcumin in treating psychiatric and neurological disorders by regulating adult neurogenesis.

**Brain-Specific Increase in Leukotriene Signaling Accompanies Chronic Neuroinflammation and Cognitive Impairment in a Model of Gulf War Illness**

Front Immunol. 2022 Apr 29; 13:853000. doi: [10.3389/fimmu.2022.853000](https://doi.org/10.3389/fimmu.2022.853000). eCollection 2022.

Sahithi Attaluri 1, Raghavendra Upadhyia 1, Maheedhar Kodali 1, Leelavathi N Madhu 1, Dinesh Upadhyia 1, Bing Shuai 1, Ashok K Shetty 1

**Affiliation**

1Institute for Regenerative Medicine, Department of Molecular and Cellular Medicine, College of Medicine, Texas A&M University Health Science Center, College Station, TX, United States.

**Abstract**

Persistent cognitive impairment is a primary central nervous system-related symptom in veterans afflicted with chronic Gulf War Illness (GWI). Previous studies in a rat model have revealed that cognitive dysfunction in chronic GWI is associated with neuroinflammation, typified by astrocyte hypertrophy, activated microglia, and enhanced proinflammatory cytokine levels. Studies in a mouse model of GWI have also shown upregulation of several phospholipids that serve as reservoirs of arachidonic acid, a precursor of leukotrienes (LTs). However, it is unknown whether altered LT signaling is a component of chronic neuroinflammatory conditions in GWI. Therefore, this study investigated changes in LT signaling in the brain of rats displaying significant cognitive impairments six months after exposure to GWI-related chemicals and moderate stress. The concentration of cysteinyl LTs (CysLTs), LTB<sub>4</sub>, and 5-Lipoxygenase (5-LOX), the synthesizing enzyme of LTs, were evaluated. CysLT and LTB<sub>4</sub> concentrations were elevated in the hippocampus and the cerebral cortex, along with enhanced 5-LOX expression in neurons and microglia. Such changes were also associated with increased proinflammatory cytokine levels in the hippocampus and the cerebral cortex. Enhanced CysLT and LTB<sub>4</sub> levels in the brain could also be gleaned from their concentrations in brain-derived extracellular vesicles in the circulating blood. The circulating blood in GWI rats displayed elevated proinflammatory cytokines with no alterations in CysLT and LTB<sub>4</sub> concentrations. The results provide new evidence that a brain-specific increase in LT signaling is another adverse alteration that potentially contributes to the maintenance of chronic neuroinflammation in GWI. Therefore, drugs capable of modulating LT signaling may reduce neuroinflammation and improve cognitive function in GWI. Additional findings demonstrate that altered LT levels in the brain could be tracked efficiently by analyzing brain-derived EVs in the circulating blood.

## **Neuroimmune signatures in chronic low back pain subtypes**

Brain. 2022 Apr 29;145(3):1098-1110. doi: [10.1093/brain/awab336](https://doi.org/10.1093/brain/awab336).

Zeynab Alshelh 1, Ludovica Brusaferrì 1, Atreyi Saha 1, Erin Morrissey 1, Paulina Knight 1, Minhae Kim 1, Yi Zhang 2, Jacob M Hooker 1, Daniel Albrecht 1, Angel Torrado-Carvajal 1 3, Michael S Placzek 1, Oluwaseun Akeju 2, Julie Price 1, Robert R Edwards 4, Jeungchan Lee 1, Roberta Sclocco 1 5, Ciprian Catana 1, Vitaly Napadow 1 4, Marco L Loggia 1

### **Affiliations**

1Department of Radiology, Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, USA.

2Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA.

3Medical Image Analysis and Biometry Laboratory, Universidad Rey Juan Carlos, Madrid, Spain.

4Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.

5Department of Radiology, Logan University, Chesterfield, MO, USA.

### **Abstract**

We recently showed that patients with different chronic pain conditions (such as chronic low back pain, fibromyalgia, migraine and Gulf War illness) demonstrated elevated brain and/or spinal cord levels of the glial marker 18-kDa translocator protein (TSPO), which suggests that neuroinflammation might be a pervasive phenomenon observable across multiple aetiologically heterogeneous pain disorders. Interestingly, the spatial distribution of this neuroinflammatory signal appears to exhibit a degree of disease specificity (e.g. with respect to the involvement of the primary somatosensory cortex), suggesting that different pain conditions may exhibit distinct 'neuroinflammatory signatures'. To explore this hypothesis further, we tested whether neuroinflammatory signal can characterize putative aetiological subtypes of chronic low back pain patients based on clinical presentation. Specifically, we explored neuroinflammation in patients whose chronic low back pain either did or did not radiate to the leg (i.e. 'radicular' versus 'axial' back pain). Fifty-four patients with chronic low back pain, 26 with axial back pain [43.7 ± 16.6 years old (mean ± SD)] and 28 with radicular back pain (48.3 ± 13.2 years old), underwent PET/MRI with <sup>11</sup>C-PBR28, a second-generation radioligand for TSPO. <sup>11</sup>C-PBR28 signal was quantified using standardized uptake values ratio (validated against volume of distribution ratio; n = 23). Functional MRI data were collected simultaneously to the <sup>11</sup>C-PBR28 data (i) to functionally localize the primary somatosensory cortex back and leg subregions; and (ii) to perform functional connectivity analyses (in order to investigate possible neurophysiological correlations of the neuroinflammatory signal). PET and functional MRI measures were compared across groups, cross-correlated with one another and with the severity of 'fibromyalgians' (i.e. the degree of pain centralization, or 'nociplastic pain'). Furthermore, statistical mediation models were used to explore possible causal relationships between these three variables. For the primary somatosensory cortex representation of back/leg, <sup>11</sup>C-PBR28 PET signal and functional connectivity to the thalamus were: (i) higher in radicular compared to axial back pain patients; (ii) positively correlated with each other; (iii) positively correlated with fibromyalgians scores, across groups; and finally (iv) fibromyalgians mediated the association between <sup>11</sup>C-PBR28 PET signal and primary somatosensory cortex-thalamus connectivity across groups. Our findings support the existence of 'neuroinflammatory signatures' that are accompanied by neurophysiological changes and correlate with clinical presentation (in particular, with the degree of nociplastic pain) in chronic pain patients. These signatures may contribute to the subtyping of distinct pain syndromes and also provide information about interindividual variability in neuroimmune brain signals, within diagnostic groups, that could eventually serve as targets for mechanism-based precision medicine approaches.

## **Dry Eye Symptoms and Signs in US Veterans With Gulf War Illness**

Am J Ophthalmol. 2022 May; 237:32-40. doi: [10.1016/j.ajo.2021.11.010](https://doi.org/10.1016/j.ajo.2021.11.010). Epub 2021 Nov 13.

Victor Sanchez 1, Brandon S Baksh 1, Kimberly Cabrera 1, Anjalee Choudhury 1, Katherine Jensen 1, Nancy Klimas 1, Anat Galor 2

### **Affiliations**

1From the New York University Grossman School of Medicine (V.S.), New York, New York; University of Miami Miller School of Medicine (B.S.B., A.C., N.K., A.G.), Miami, Florida; Ophthalmology, Miami Veterans Affairs Medical Center (K.C.), Miami, Florida; and Bascom Palmer Eye Institute, University of Miami (A.C., A.G.), Miami, Florida, USA.

2From the New York University Grossman School of Medicine (V.S.), New York, New York; University of Miami Miller School of Medicine (B.S.B., A.C., N.K., A.G.), Miami, Florida; Ophthalmology, Miami Veterans Affairs Medical Center (K.C.), Miami, Florida; and Bascom Palmer Eye Institute, University of Miami (A.C., A.G.), Miami, Florida, USA. Electronic address: [agalor@med.miami.edu](mailto:agalor@med.miami.edu).

### **Abstract**

**Purpose:** To examine dry eye (DE) symptoms and signs in individuals with vs without Gulf War illness (GWI).

**Design:** Prospective cross-sectional study.

**Methods:** We performed a prospective, cross-sectional study of South Florida veterans who were active duty during the Gulf War era (GWE; 1990-1991) and seen at an eye clinic between October 1, 2020, and March 13, 2021. Veterans were split into 2 groups: those who met Kansas criteria for GWI (cases, n = 30) and those who did not (controls, n = 41). DE symptoms were assessed via standardized questionnaires whereas DE signs were assessed using a series of ocular surface parameters. Differences between groups were assessed via Mann-Whitney U test. Linear regression analyses were used to examine which GWI symptoms most closely aligned with DE symptoms.

**Results:** Veterans with GWI had higher DE symptoms scores compared to controls (Ocular Surface Disease Index [OSDI] scores: mean  $41.20 \pm 22.92$  vs  $27.99 \pm 24.03$ ,  $P = .01$ ). In addition, veterans with GWI had higher eye pain scores compared with controls (average eye pain over past week:  $2.63 \pm 2.72$  vs  $1.22 \pm 1.50$ ,  $P = .03$ ), including on neuropathic ocular pain questionnaires (Neuropathic Pain Symptom Inventory modified for the Eye [NPSI-E]:  $17.33 \pm 17.20$  vs  $9.63 \pm 12.64$ ,  $P = .03$ ). DE signs were mostly similar between the groups. GWI symptoms "nausea or upset stomach" ( $\beta = 14.58$ ,  $SE = 3.02$ ,  $P < .001$ ) and "headache" ( $\beta = 7.90$ ,  $SE = 2.91$ ,  $P = .011$ ) correlated with higher OSDI scores.

**Conclusion:** Individuals with GWI have more severe DE symptoms and ocular pain scores but similar tear and ocular surface parameters compared to controls without GWI. This finding suggests that mechanisms beyond tear dysfunction drive eye symptoms in GWI.



**Invited Perspective: Causal Implications of Gene by Environment Studies Applied to Gulf War Illness**

Environ Health Perspect. 2022 May;130(5):51301. doi: [10.1289/EHP11057](https://doi.org/10.1289/EHP11057). Epub 2022 May 11.

Marc G Weisskopf 1, Kimberly A Sullivan 2

**Affiliations**

1Departments of Environmental Health and Epidemiology, Harvard TH Chan School of Public Health, Boston, Massachusetts, USA.

2Department of Environmental Health, Boston University School of Public Health, Boston, Massachusetts, USA.

**No abstract available**

**Evaluation of a Gene-Environment Interaction of PON1 and Low-Level Nerve Agent Exposure with Gulf War Illness: A Prevalence Case-Control Study Drawn from the U.S. Military Health Survey's National Population Sample**

Environ Health Perspect. 2022 May;130(5):57001. doi: [10.1289/EHP9009](https://doi.org/10.1289/EHP9009). Epub 2022 May 11.

Robert W Haley 1, Gerald Kramer 1, Junhui Xiao 1, Jill A Dever 2, John F Teiber 1

**Affiliations**

1Division of Epidemiology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA.

2RTI International, Washington, District of Columbia, USA.

**Abstract**

**Background:** Consensus on the etiology of 1991 Gulf War illness (GWI) has been limited by lack of objective individual-level environmental exposure information and assumed recall bias.

**Objectives:** We investigated a prestated hypothesis of the association of GWI with a gene-environment (GxE) interaction of the paraoxonase-1 (PON1) Q192R polymorphism and low-level nerve agent exposure.

**Methods:** A prevalence sample of 508 GWI cases and 508 nonpaired controls was drawn from the 8,020 participants in the U.S. Military Health Survey, a representative sample survey of military veterans who served during the Gulf War. The PON1 Q192R genotype was measured by real-time polymerase chain reaction (RT-PCR), and the serum Q and R isoenzyme activity levels were measured with PON1-specific substrates. Low-level nerve agent exposure was estimated by survey questions on having heard nerve agent alarms during deployment.

**Results:** The GxE interaction of the Q192R genotype and hearing alarms was strongly associated with GWI on both the multiplicative [prevalence odds ratio (POR) of the interaction = 3.41; 95% confidence interval (CI): 1.20, 9.72] and additive (synergy index = 4.71; 95% CI: 1.82, 12.19) scales, adjusted for measured confounders. The Q192R genotype and the alarms variable were independent (adjusted POR in the controls = 1.18; 95% CI: 0.81, 1.73;  $p = 0.35$ ), and the associations of GWI with the number of R alleles and quartiles of Q isoenzyme were monotonic. The adjusted relative excess risk due to interaction (aRERI) was 7.69 (95% CI: 2.71, 19.13). Substituting Q isoenzyme activity for the genotype in the analyses corroborated the findings. Sensitivity analyses suggested that recall bias had forced the estimate of the GxE interaction toward the null and that unmeasured confounding is unlikely to account for the findings. We found a GxE interaction involving the Q-correlated PON1 diazoxonase activity and a weak possible GxE involving the Khamisiyah plume model, but none involving the PON1 R isoenzyme activity, arylesterase activity, paraoxonase activity, butyrylcholinesterase genotypes or enzyme activity, or pyridostigmine.

**Discussion:** Given gene-environment independence and monotonicity, the unconfounded aRERI >0 supports a mechanistic interaction. Together with the direct evidence of exposure to fallout from bombing of chemical weapon storage facilities and the extensive toxicologic evidence of biochemical protection from organophosphates by the Q isoenzyme, the findings provide strong evidence for an etiologic role of low-level nerve agent in GWI. <https://doi.org/10.1289/EHP9009>.

## Regulatory Modulations and Dendritic Arborization in the Mouse Hippocampus Following Gulf War Toxicant Exposure

FASEB J. 2022 May;36 Suppl 1. doi: [10.1096/fasebj.2022.36.S1.R5728](https://doi.org/10.1096/fasebj.2022.36.S1.R5728).

Kathleen E Murray 1 2, Whitney A Ratliff 3, Vedad Delic 1 4, Bruce A Citron 1 2 5

### Affiliations

1Laboratory of Molecular Biology, Research & Development, Department of Veterans Affairs, VA New Jersey Health Care System, East Orange, NJ.

2Rutgers School of Graduate Studies, Newark, NJ.

3Laboratory of Molecular Biology, Research & Development, Department of Veterans Affairs, Bay Pines VA Healthcare System, Bay Pines, FL.

4Pharmacology, Physiology, and Neuroscience, Rutgers-New Jersey Medical School, East Orange, NJ.

5Pharmacology, Physiology, and Neuroscience, Rutgers-New Jersey Medical School, Newark, NJ.

### Abstract

Gulf War illness (GWI) is a chronic multi-symptom syndrome which affects approximately 30% of the nearly 700,000 Veterans who were deployed to the Persian Gulf from 1990 to 1991. These Veterans have reported experiencing a variety of symptoms including difficulties with learning and memory, depression and anxiety, and increased incidence of neurodegenerative diseases. Evidence suggests that combined exposure to both reversible and irreversible acetylcholinesterase (AChE) inhibitors is a likely risk factor. We modeled Gulf War exposure in male C57Bl/6J mice with three AChE inhibitors that have been implicated as causative agents for GWI: pyridostigmine bromide (PB), the anti-sarin prophylactic; chlorpyrifos (CPF), an organophosphate insecticide; and N,N-diethyl-m-toluamide (DEET), a common insect repellent. Previously, we reported acute hippocampal gene expression changes following 10 d of toxicant exposure, including significant downregulation of several neuronal immediate early genes (IEGs) such as *Arc*, *Egr1*, and *Nr4a1*, as well as hippocampal-dependent memory impairment in a Y-maze task. *Arc* is predominantly expressed in cortical and hippocampal neurons and is critical for long-term potentiation (LTP) and stabilization of synaptic plasticity. IEGs such as *Arc* and *Egr1* have also been suggested to play a role in determining the risk of developing major depressive disorder, which is often comorbid with GWI. Here, we quantified *Arc* protein expression in granule cells of the dentate gyrus with IHC at 2-4 h post-exposure and examined the effects of treatment with a neuroprotective Nrf2 activator, tert-butylhydroquinone (tBHQ), at 14 weeks post-exposure. Additionally, mice were either placed in a novel enriched environment for 5 min or kept in their home cage to evaluate induced *Arc* expression in granule cells at 4 h post-exposure. We also assessed dendritic arborization, important in connectivity, in granule cells by measuring dendritic lengths and spine densities with Golgi staining at 12 weeks post-exposure. We hypothesized that toxicant-exposed mice would have fewer *Arc*+ granule cells in the dentate gyrus and show reductions in both basal and induced *Arc* expression at 4 h post-exposure. We also hypothesized that exposed mice would display dendritic arbor reduction and loss of spines in granule cells at the chronic timepoint, and that this effect would be reversed by antioxidant treatment. Preliminary results indicate that *Arc* protein expression is decreased in granule cells of exposed mice at the acute but not chronic timepoint. Dendritic arbor complexity was significantly reduced at the chronic phase in exposed mice but improved when treated with 1% tBHQ formulated food pellets. Our results suggest that IEGs may only be dysregulated immediately following exposure but could contribute to long-term detrimental effects on hippocampal neuroplasticity, which may be improved with antioxidant treatment.

## Utility of the ALSFRS-R for predicting ALS and comorbid disease neuropathology: The Veterans Affairs Biorepository Brain Bank

Muscle Nerve. 2022 May 18. doi: [10.1002/mus.27635](https://doi.org/10.1002/mus.27635). Online ahead of print.

Leigh E Colvin 1, Zachariah W Foster 1, Thor D Stein 1 2 3 4 5, Manisha Thakore-James 1 6, Mohammad Kian Salajegheh 1 7, Kendall Carr 1, Keith R Spencer 1, Nazifa Abdul Rauf 1, Latease Adams 1, James G Averill 8, Sean E Walker 8, Ian Robey 8, Victor E Alvarez 1 2 3 4 6, Bertrand R Huber 1 2 3 4 6, Ann C McKee 1 2 3 4 5 6, Neil W Kowall 1 2 3 6, Christopher B Brady 1 2 6 7

### Affiliations

1VA Boston Healthcare System, Boston, Massachusetts, USA.

2Boston University School of Medicine, Boston, Massachusetts, USA.

3Boston University Alzheimer's Disease and CTE Center, Boston University School of Medicine, Boston, Massachusetts, USA.

4Department of Veterans Affairs Medical Center, Bedford, Massachusetts, USA.

5Department of Pathology and Laboratory Medicine, Boston University School of Medicine, Boston, Massachusetts, USA.

6Department of Neurology, Boston University School of Medicine, Boston, Massachusetts, USA.

7Harvard Medical School, Boston, Massachusetts, USA.

8Southern Arizona VA Healthcare System, Tucson, Arizona, USA.

### Abstract

**Introduction/aims:** The amyotrophic lateral sclerosis (ALS) functional rating scale-revised (ALSFRS-R) is commonly used to track ALS disease progression; however, there are gaps in the literature regarding the extent to which the ALSFRS-R relates to underlying central nervous system (CNS) pathology. The current study explored the association between ALSFRS-R (total and subdomain) scores and postmortem neuropathology (both ALS-specific and comorbid disease).

**Methods:** Within our sample of 93 military veterans with autopsy-confirmed ALS, we utilized hierarchical cluster analysis (HCA) to identify discrete profiles of motor dysfunction based on ALSFRS-R subdomain scores. We examined whether emergent clusters were associated with neuropathology. Separate analyses of variance and covariance with post-hoc comparisons were performed to examine relevant cluster differences.

**Results:** Analyses revealed significant correlations between ALSFRS-R total and subdomain scores with some, but not all, neuropathological variables. The HCA illustrated three groups: Cluster 1-predominantly diffuse functional impairment; Cluster 2-spared respiratory/bulbar and impaired motor function; and Cluster 3-spared bulbar and impaired respiratory, and fine and gross motor function. Individuals in Cluster 1 (and to a lesser degree, Cluster 3) exhibited greater accumulation of ALS-specific neuropathology and less comorbid neuropathology than those in Cluster 2.

**Discussion:** These results suggest that discrete patterns of motor dysfunction based on ALSFRS-R subdomain scores are related to postmortem neuropathology. Findings support use of ALSFRS-R subdomain scores to capture the heterogeneity of clinical presentation and disease progression in ALS, and may assist researchers in identifying endophenotypes for separate assessment in clinical trials.

**Comment on "Evaluation of a Gene-Environment Interaction of PON1 and Low-Level Nerve Agent Exposure with Gulf War Illness: A Prevalence Case-Control Study Drawn from the U.S. Military Health Survey's National Population Sample"**

Environ Health Perspect. 2022 Jun;130(6):68003. doi: [10.1289/EHP11558](https://doi.org/10.1289/EHP11558). Epub 2022 Jun 15.

David Curtis 1 2

**Affiliations**

1UCL Genetics Institute, University College London, London, UK.

2Centre for Psychiatry, Queen Mary University of London, London, UK.

PMID: 35703987 PMCID: PMC9199865 DOI: [10.1289/EHP11558](https://doi.org/10.1289/EHP11558)

**No abstract available**

**Response to "Comment on 'Evaluation of a Gene-Environment Interaction of PON1 and Low-Level Nerve Agent Exposure with Gulf War Illness: A Prevalence Case-Control Study Drawn from the U.S. Military Health Survey's National Population Sample'"**

Environ Health Perspect. 2022 Jun;130 (6):68004. doi: [10.1289/EHP11607](https://doi.org/10.1289/EHP11607). Epub 2022 Jun 15.

Robert W Haley 1, Jill A Dever 2, John F Teiber 1

**Affiliations**

1University of Texas Southwestern Medical Center, Dallas, Texas, USA.

2RTI International, Research Triangle Park, North Carolina, USA.

**No abstract available**

**Response to "Comment on 'Evaluation of a Gene-Environment Interaction of PON1 and Low-Level Nerve Agent Exposure with Gulf War Illness: A Prevalence Case-Control Study <https://pubmed.ncbi.nlm.nih.gov/35703988/Drawn> from the U.S. Military Health Survey's National Population Sample'"**

Environ Health Perspect. 2022 Jun;130(6):68005. doi: [10.1289/EHP11614](https://doi.org/10.1289/EHP11614). Epub 2022 Jun 15.

Marc G Weisskopf 1 2

**Affiliations**

1Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA.

2Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA.

**No abstract available**

**Host gut resistome in Gulf War chronic multisymptom illness correlates with persistent inflammation**

Commun Biol. 2022 Jun 7;5(1):552. doi: [10.1038/s42003-022-03494-7](https://doi.org/10.1038/s42003-022-03494-7).

Dipro Bose # 1, Somdatta Chatterjee # 1, Ethan Older # 2, Ratanesh Seth 1, Patricia Janulewicz 3, Punng Saha 1, Ayan Mondal 1, Jeffrey M Carlson 3, Alan W Decho 1, Kimberly Sullivan 3, Nancy Klimas 4, Stephen Lasley 5, Jie Li 2, Saurabh Chatterjee 6 7

**Affiliations**

1Environmental Health and Disease Laboratory, Department of Environmental Health Sciences, Arnold School of Public Health, University of South Carolina, Columbia, SC, USA.

2Department of Chemistry and Biochemistry, University of South Carolina, Columbia, SC, USA.

3Department of Environmental Health, Boston University School of Public Health, Boston, MA, USA.

4Department of Clinical Immunology, Nova Southeastern University, Fort Lauderdale, FL, USA.

5Department of Cancer Biology and Pharmacology, University of Illinois College of Medicine, Peoria, IL, USA.

6Environmental Health and Disease Laboratory, Department of Environmental Health Sciences, Arnold School of Public Health, University of South Carolina, Columbia, SC, USA. [schatt@mailbox.sc.edu](mailto:schatt@mailbox.sc.edu).

7Columbia VA Medical Center, Columbia, SC, USA. [schatt@mailbox.sc.edu](mailto:schatt@mailbox.sc.edu).

#Contributed equally.

**Abstract**

Chronic multisymptom illness (CMI) affects a subsection of elderly and war Veterans and is associated with systemic inflammation. Here, using a mouse model of CMI and a group of Gulf War (GW) Veterans' with CMI we show the presence of an altered host resistome. Results show that antibiotic resistance genes (ARGs) are significantly altered in the CMI group in both mice and GW Veterans when compared to control. Fecal samples from GW Veterans with persistent CMI show a significant increase of resistance to a wide class of antibiotics and exhibited an array of mobile genetic elements (MGEs) distinct from normal healthy controls. The altered resistome and gene signature is correlated with mouse serum IL-6 levels. Altered resistome in mice also is correlated strongly with intestinal inflammation, decreased synaptic plasticity, reversible with fecal microbiota transplant (FMT). The results reported might help in understanding the risks to treating hospital acquired infections in this population.



## Pain, but not Physical Activity, is Associated with Gray Matter Volume Differences in Gulf War Veterans with Chronic Pain

J Neurosci. 2022 Jun 13; JN-RM-2394-21. doi: [10.1523/JNEUROSCI.2394-21.2022](https://doi.org/10.1523/JNEUROSCI.2394-21.2022). Online ahead of print.

Jacob V Ninneman 1 2, Nicholas P Gretzon 1 2, Aaron J Stegner 1 2, Jacob B Lindheimer 1 2, Michael J Falvo 3, Glenn Wylie 3 4 5, Ryan J Dougherty 6, Neda E Almassi 1 2, Stephanie M Van Riper 7, Alexander E Boruch 1 2, Douglas C Dean 3rd 2, Kelli F Koltyn 2, Dane B Cook 8 2

### Affiliations

1William S. Middleton Memorial Veterans Hospital, Madison, WI, 53705.

2University of Wisconsin-Madison, Madison, WI, 53706.

3War Related Illness and Injury Study Center, Department of Veterans Affairs, New Jersey Health Care System, East Orange, NJ, 07018.

4Kessler Foundation, West Orange, NJ, 07052.

5Rutgers University, Newark, NJ, 08854.

6Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA, 21287.

7Stanford University School of Medicine, Stanford, California, 94301.

8William S. Middleton Memorial Veterans Hospital, Madison, WI, 53705. [dane.cook@wisc.edu](mailto:dane.cook@wisc.edu).

### Abstract

Chronic musculoskeletal pain (CMP) is a significant burden for Persian Gulf War Veterans (GWV), yet the causes are poorly understood. Brain structure abnormalities are observed in GWV, however relationships with modifiable lifestyle factors such as physical activity (PA) are unknown. We evaluated gray matter volumes and associations with symptoms, PA, and sedentary time in GWV with and without CMP. Ninety-eight GWV (10 females) with CMP and 56 GWV (7 females) controls completed T1 weighted magnetic resonance imaging, pain and fatigue symptom questionnaires, and PA measurement via actigraphy. Regional gray matter volumes were analyzed using voxel-based morphometry and were compared across groups using analysis of covariance. Separate multiple linear regression models were used to test associations between PA intensities, sedentary time, symptoms, and gray matter volumes. Family-wise cluster error rates were used to control for multiple comparisons ( $\alpha=0.05$ ). GWV with CMP reported greater pain and fatigue symptoms, worse mood, and engaged in less moderate-to-vigorous PA and more sedentary time than healthy GWV (all  $p<0.05$ ). GWV with CMP had smaller gray matter volumes in the bilateral insula and larger volumes in the frontal pole ( $p<0.05$ adjusted). Gray matter volumes in the left insula were associated with pain symptoms ( $r_{\text{partial}}=0.26, -0.29; p<0.05$ adjusted). No significant associations were observed for either PA or sedentary time ( $p>0.05$ adjusted). GWV with CMP had smaller gray matter volumes within a critical brain region of the descending pain processing network and larger volumes within brain regions associated with pain sensation and affective processing which may reflect pain chronification. **Significance Statement:** The pathophysiology of chronic pain in Gulf War Veterans is understudied and not well understood. In a large sample of Gulf War Veterans, we report Veterans with chronic musculoskeletal pain have smaller gray matter volumes in brain regions associated with pain regulation and larger volumes in regions associated with pain sensitivity compared to otherwise healthy Gulf War Veterans. Gray matter volumes in regions of pain regulation were significantly associated with pain symptoms and encompassed the observed group brain volume differences. These results are suggestive of deficient pain modulation that may contribute to pain chronification.

**Nutrient Intake as a Predictor of Health Improvement on the Low Glutamate Diet in Veterans With Gulf War Illness (GWI)**

Current Developments in Nutrition, Volume 6, Issue Supplement\_1, June 2022, Page 806, doi.org/10.1093/cdn/nzac064.025 Published: 14 June 2022

Shalini Ramachandra, Kathleen Holton

**Affiliations**

American University

**Abstract**

**Objectives**

Gulf War Illness (GWI) is a chronic multi-symptom condition characterized by widespread chronic pain, fatigue, cognitive dysfunction, and mood dysregulation. Previous research found that the low glutamate diet can reduce overall symptoms of GWI, including systemic inflammation. Micronutrients thought to be protective against excitotoxicity include riboflavin, vitamins B6, C, D, and E, and magnesium. This research examined whether changes in these micronutrients after one month on the low glutamate diet could predict overall improvement in GWI symptoms, after accounting for changes in free glutamate intake.

**Methods**

Forty veterans with GWI were recruited, and three-day food diaries, among other health measurements, were collected at baseline and after one month on the low glutamate diet. Nutrition Data Systems for Research was used to analyze dietary intake data. Dietary adherence was measured with a glutamate food frequency questionnaire (FFQ), and improvement on the diet was defined as being “much/very much” improved on the patient global impression of change scale (PGIC) or as having  $\geq 30\%$  of their symptoms remit. Logistic regression was used to model improvement on the diet, after adjusting for age, sex, change in FFQ, and change in BMI.

**Results**

Increased vitamin C intake significantly predicted improvement based on  $\geq 30\%$  symptom remission ( $p = 0.02$ ). Similarly, increased intake of vitamin E and magnesium each marginally predicted improvement based on the PGIC (both  $p = 0.06$ ).

**Conclusions**

These findings suggest that in addition to reduction in free glutamate consumption, improved intake of vitamin C, vitamin E, and magnesium, may be driving improvement in neurological symptoms on the low glutamate diet. Further research is warranted.