

[Results of a RCT assessing saline and xylitol nasal irrigation for CRS and fatigue in Gulf War illness](#)

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Abstract

Objective: To assess the efficacy of saline nasal irrigation (S-NI) and xylitol nasal irrigation (X-NI) for chronic rhinosinusitis in participants with Gulf War illness (GWI).

Methods: This 26 week, 3-arm (1:1:1) randomized controlled trial examined veterans meeting criteria for GWI with moderate-to-severe chronic rhinosinusitis and fatigue symptoms. All participants received standard of care for chronic rhinosinusitis (CRS); additionally, S-NI or X-NI participants added twice-daily NI using 2% saline or 5% xylitol solutions. Outcomes included disease-specific quality of life (primary; sino-nasal outcome test [SNOT-20]; 0-100 points), overall quality of life (Short-Form 36), and fatigue (Multidimensional Fatigue Index). Outcome assessors were blind to allocation group. Intention-to-treat analysis used repeated measures modeling; statistical significance was evaluated at the two-sided α level of .05.

Results: Randomization (N = 40) produced three similar groups regarding sex (male, 80%), age (53.8 ± 7.8 years), duration (19.8 ± 7.7 years), and illness severity (48.5 ± 12.7 SNOT-20 points). Age- and gender-adjusted between-group comparison showed that X-NI participants, compared with control, reported improved SNOT-20 scores at 8 weeks (13.5 points, 95% confidence interval [CI] -27.9 to 0.9) and at 26 weeks (15.4 points, 95% CI -30.1 to -0.6). S-NI participants improved by 13.4 points (95% CI -28.8, 2.1) at 26 weeks compared with control. The improvement in both NI groups approached minimal clinical important difference compared to control for the SNOT-20 in the general population. Secondary outcomes were not different between groups. Satisfaction in both irrigation groups was high.

Conclusions: This randomized controlled trial suggests that NI with saline or xylitol improves chronic sinus symptoms among participants with GWI with improvement scores similar to those in the general population.

Level of evidence: 1b, individual randomized controlled trial.

[Gulf war illness, post-HPV vaccination syndrome, and Macrophagic Myofasciitis. Similar disabling conditions possibly linked to vaccine-induced autoimmune dysautonomia](#)

Autoimmun Rev. 2020 Jul 10;102603. doi: 10.1016/j.autrev.2020.102603. Online ahead of print.

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Abstract

More than one-fourth of all Persian gulf war coalition soldiers remain seriously ill. Several epidemiological studies suggest a link between multiple vaccinations at the time of the military operation and the illness development. Macrophagic Myofasciitis and post-HPV vaccination syndrome are two newer controversial vaccine-related disabling ailments.

Objectives: 1) To systematically review all original articles investigating the association of vaccines with gulf war illness, 2) To discuss gulf war illness, Macrophagic Myofasciitis, and post-HPV vaccination syndrome clinical similarities, 3) To discuss emergent pathogenetic mechanisms proposed for post-HPV vaccination syndrome that may be also relevant to gulf war illness and Macrophagic Myofasciitis.

Results: All original epidemiological studies (n = 11) found a positive association between vaccination and gulf war illness development. Chronic fatigue, widespread pain and cognitive impairment characterize the three syndromes under discussion. Anti-adrenergic receptor antibodies, dysautonomia and small fiber neuropathy have been recently described in patients with post-HPV vaccination syndrome.

Conclusion: post-HPV vaccination syndrome, Macrophagic Myofasciitis, and gulf war illness analogy suggests that some vaccines or multiple vaccinations in a very short period of time may induce, in susceptible individuals, chronic pain, fatigue and dyscognition. Vaccine-induced autoimmune dysautonomia is hypothesized as the common pathogenetic mechanism for this symptom cluster. Further research on the presence of small fiber neuropathy, adrenergic receptor antibodies, and abnormal autonomic function tests in the three syndromes under discussion may help to elucidate this hypothesis.

[Machine Learning Detects Pattern of Differences in Functional Magnetic Resonance Imaging \(fMRI\) Data between Chronic Fatigue Syndrome \(CFS\) and Gulf War Illness \(GWI\)](#)

Brain Sci. 2020 Jul 17;10(7):E456. doi: 10.3390/brainsci10070456.

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Abstract

Background: Gulf War Illness (GWI) and Chronic Fatigue Syndrome (CFS) are two debilitating disorders that share similar symptoms of chronic pain, fatigue, and exertional exhaustion after exercise. Many physicians continue to believe that both are psychosomatic disorders and to date no underlying etiology has been discovered. As such, uncovering objective biomarkers is important to lend credibility to criteria for diagnosis and to help differentiate the two disorders.

Methods: We assessed cognitive differences in 80 subjects with GWI and 38 with CFS by comparing corresponding fMRI scans during 2-back working memory tasks before and after exercise to model brain activation during normal activity and after exertional exhaustion, respectively. Voxels were grouped by the count of total activity into the Automated Anatomical Labeling (AAL) atlas and used in an "ensemble" series of machine learning algorithms to assess if a multi-regional pattern of differences in the fMRI scans could be detected.

Results: A K-Nearest Neighbor (70%/81%), Linear Support Vector Machine (SVM) (70%/77%), Decision Tree (82%/82%), Random Forest (77%/78%), AdaBoost (69%/81%), Naïve Bayes (74%/78%), Quadratic Discriminant Analysis (QDA) (73%/75%), Logistic Regression model (82%/82%), and Neural Net (76%/77%) were able to differentiate CFS from GWI before and after exercise with an average of 75% accuracy in predictions across all models before exercise and 79% after exercise. An iterative feature selection and removal process based on Recursive Feature Elimination (RFE) and Random Forest importance selected 30 regions before exercise and 33 regions after exercise that differentiated CFS from GWI across all models, and produced the ultimate best accuracies of 82% before exercise and 82% after exercise by Logistic Regression or Decision Tree by a single model, and 100% before and after exercise when selected by any six or more models. Differential activation on both days included the right anterior insula, left putamen, and bilateral orbital frontal, ventrolateral prefrontal cortex, superior, inferior, and precuneus (medial) parietal, and lateral temporal regions. Day 2 had the cerebellum, left supplementary motor area and bilateral pre- and post-central gyri. Changes between days included the right Rolandic operculum switching to the left on Day 2, and the bilateral midcingulum switching to the left anterior cingulum.

Conclusion: We concluded that CFS and GWI are significantly differentiable using a pattern of fMRI activity based on an ensemble machine learning model.

[The Innate Immune System and Inflammatory Priming: Potential Mechanistic Factors in Mood Disorders and Gulf War Illness](#)

Front Psychiatry. 2020 Jul 23;11:704. doi: 10.3389/fpsy.2020.00704.eCollection 2020.

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Abstract

Gulf War Illness is a chronic multisystem disorder affecting approximately a third of the Veterans of the Gulf War, manifesting with physical and mental health symptoms such as cognitive impairment, neurological abnormalities, and dysregulation of mood. Among the leading theories into the etiology of this multisystem disorder is environmental exposure to the various neurotoxins encountered in the Gulf Theatre, including organophosphates, nerve agents, pyridostigmine bromide, smoke from oil well fires, and depleted uranium. The relationship of toxin exposure and the pathogenesis of Gulf War Illness converges on the innate immune system: a nonspecific form of immunity ubiquitous in nature that acts to respond to both exogenous and endogenous insults. Activation of the innate immune system results in inflammation mediated by the release of cytokines. Cytokine mediated neuroinflammation has been demonstrated in a number of psychiatric conditions and may help explain the larger than expected population of Gulf War Veterans afflicted with a mood disorder. Several of the environmental toxins encountered by soldiers during the first Gulf War have been shown to cause upregulation of inflammatory mediators after chronic exposure, even at low levels. This act of inflammatory priming, by which repeated exposure to chronic subthreshold insults elicits robust responses, even after an extended period of latency, is integral in the connection of Gulf War Illness and comorbid mood disorders. Further developing the understanding of the relationship between environmental toxin exposure, innate immune activation, and pathogenesis of disease in the Gulf War Veterans population, may yield novel therapeutic targets, and a greater understanding of disease pathology and subsequently prevention.

[Host *Akkermansia muciniphila* Abundance Correlates With Gulf War Illness Symptom Persistence via NLRP3-Mediated Neuroinflammation and Decreased Brain-Derived Neurotrophic Factor](#)

Neurosci Insights. 2020 Jul 27;15:2633105520942480. doi: 10.1177/2633105520942480. eCollection 2020.

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- PMID: [32832901](#)
 - PMCID: [PMC7440889](#)
 - DOI: [10.1177/2633105520942480](#)

Abstract

Neurological disorders are commonly reported among veterans who returned from the Gulf war. Veterans who suffer from Gulf War illness (GWI) complain of continued symptom persistence that includes neurological disorders, muscle weakness, headaches, and memory loss, that developed during or shortly after the war. Our recent research showed that chemical exposure associated microbial dysbiosis accompanied by a leaky gut connected the pathologies in the intestine, liver, and brain. However, the mechanisms that caused the symptoms to persist even 30 years after the war remained elusive to investigators. In this study, we used a rodent model of GWI to investigate the persistence of microbiome alterations, resultant chronic inflammation, and its effect on neurotrophic and synaptic plasticity marker BDNF. The results showed that exposure to GW chemicals (the pesticide permethrin and prophylactic drug pyridostigmine bromide) resulted in persistent pathology characterized by the low relative abundance of the probiotic bacteria *Akkermansia muciniphila* in the gut, which correlated with high circulatory HMGB1 levels, blood-brain barrier dysfunction, neuroinflammation and lowered neurotrophin BDNF levels. Mechanistically, we used mice lacking the NLRP3 gene to investigate this inflammasome's role in observed pathology. These mice had significantly decreased inflammation and a subsequent increase in BDNF in the frontal cortex. This suggests that a persistently low species abundance of *Akkermansia muciniphila* and associated chronic inflammation due to inflammasome activation might be playing a significant role in contributing to chronic neurological problems in GWI. A therapeutic approach with various small molecules that can target both the restoration of a healthy microbiome and decreasing inflammasome activation might have better outcomes in treating GWI symptom persistence.

[Alterations in high-order diffusion imaging in veterans with Gulf War Illness is associated with chemical weapons exposure and mild traumatic brain injury](#)

Brain Behav Immun. 2020 Jul 31;S0889-1591(20)30307-X. doi: 10.1016/j.bbi.2020.07.006. Online ahead of print.

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Abstract

The complex etiology behind Gulf War Illness (GWI) has been attributed to the combined exposure to neurotoxicant chemicals, brain injuries, and some combat experiences. Chronic GWI symptoms have been shown to be associated with intensified neuroinflammatory responses in animal and human studies. To investigate the neuroinflammatory responses and potential causes in Gulf War (GW) veterans, we focused on the effects of chemical/biological weapons (CBW) exposure and mild traumatic brain injury (mTBI) during the war. We applied a novel MRI diffusion processing method, Neurite density imaging (NDI), on high-order diffusion imaging to estimate microstructural alterations of brain imaging in Gulf War veterans with and without GWI, and collected plasma proinflammatory cytokine samples as well as self-reported health symptom scores. Our study identified microstructural changes specific to GWI in the frontal and limbic regions due to CBW and mTBI, and further showed distinctive microstructural patterns such that widespread changes were associated with CBW and more focal changes on diffusion imaging were observed in GW veterans with an mTBI during the war. In addition, microstructural alterations on brain imaging correlated with upregulated blood proinflammatory cytokine markers TNFR1 and TNFR2 and with worse outcomes on self-reported symptom measures for fatigue and sleep functioning. Taken together, these results suggest TNF signaling mediated inflammation affects frontal and limbic regions of the brain, which may contribute to the fatigue and sleep symptoms of the disease and suggest a strong neuroinflammatory component to GWI. These results also suggest exposures to chemical weapons and mTBI during the war are associated with different patterns of peripheral and central inflammation and highlight the brain regions vulnerable to further subtle microscale morphological changes and chronic signaling to nearby glia.

[Pyridostigmine bromide exposure creates chronic, underlying neuroimmune disruption in the gastrointestinal tract and brain that alters responses to palmitoylethanolamide in a mouse model of Gulf War Illness](#)

Neuropharmacology. 2020 Aug 3;108264. doi: 10.1016/j.neuropharm.2020.108264. Online ahead of print.

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Abstract

Gulf War Illness (GWI) is a chronic multisymptom illness that includes gastrointestinal disorders. Although the exact etiology of GWI is unknown, exposure to the drug pyridostigmine bromide (PB) is considered a major factor. Exposure to PB drives enteric neuroinflammation, promotes immunosuppression, and alters physiological functions of the colon in the short term but whether exposure to PB is sufficient to promote long term dysfunction is not known. Here, we tested whether exposure to PB is sufficient to drive long term changes that reflect GWI, and whether the endogenous anti-inflammatory mediator palmitoylethanolamide (PEA) is sufficient to reduce the detrimental effects of PB in the gut and brain of mice. Exposure to PB alone was not sufficient to cause major changes in neuromuscular transmission but did drive major changes by altering the effects of PEA. Calcium imaging data show that the mechanisms responsible include a shift in receptor signaling mediated by TRPV1, endocannabinoids, and peroxisome proliferator-activated receptors alpha (PPAR α). Additional mechanisms include the development of glial reactivity and changes in enteric neurochemical coding and survival. PB and PEA caused major shifts in pro-inflammatory cytokines/chemokines in the brain and colon that persisted up to 5 months following exposure. Many of the effects of PB and PEA exhibit significant sex differences. Together, these results highlight novel mechanisms whereby PB promotes long-lasting changes in nervous system and immune function by inducing occult neuroplasticity that is revealed by subsequent exposure to unrelated drugs in a sex dependent manner.

TLR Antagonism by Sparstolonin B Alters Microbial Signature and Modulates Gastrointestinal and Neuronal Inflammation in Gulf War Illness Preclinical Model

Brain Sci. 2020 Aug 8;10(8):E532. doi: 10.3390/brainsci10080532.

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- PMID: [32784362](#)
- DOI: [10.3390/brainsci10080532](#)

Abstract

The 1991 Persian Gulf War veterans presented a myriad of symptoms that ranged from chronic pain, fatigue, gastrointestinal disturbances, and cognitive deficits. Currently, no therapeutic regimen exists to treat the plethora of chronic symptoms though newer pharmacological targets such as microbiome have been identified recently. Toll-like receptor 4 (TLR4) antagonism in systemic inflammatory diseases have been tried before with limited success, but strategies with broad-spectrum TLR4 antagonists and their ability to modulate the host-microbiome have been elusive. Using a mouse model of Gulf War Illness, we show that a nutraceutical, derived from a Chinese herb Sparstolonin B (SsnB) presented a unique microbiome signature with an increased abundance of butyrogenic bacteria. SsnB administration restored a normal tight junction protein profile with an increase in Occludin and a parallel decrease in Claudin 2 and inflammatory mediators high mobility group box 1 (HMGB1), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6) in the distal intestine. SsnB also decreased neuronal inflammation by decreasing IL-1 β and HMGB1, while increasing brain-derived neurotrophic factor (BDNF), with a parallel decrease in astrocyte activation in vitro. Mechanistically, SsnB inhibited the binding of HMGB1 and myeloid differentiation primary response protein (MyD88) to TLR4 in the intestine, thus attenuating TLR4 downstream signaling. Studies also showed that SsnB was effective in suppressing TLR4-induced nod-like receptor protein 3 (NLRP3) inflammasome activation, a prominent inflammatory disease pathway. SsnB significantly decreased astrocyte activation by decreasing colocalization of glial fibrillary acid protein (GFAP) and S100 calcium-binding protein B (S100B), a crucial event in neuronal inflammation. Inactivation of SsnB by treating the parent molecule by acetate reversed the deactivation of NLRP3 inflammasome and astrocytes in vitro, suggesting that SsnB molecular motifs may be responsible for its anti-inflammatory activity.

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[Exercise alters brain activation in Gulf War Illness and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome](#)

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- PMID: [32954325](#)
- PMCID: [PMC7425336](#)
- DOI: [10.1093/braincomms/fcaa070](#)

Abstract

Gulf War Illness affects 25-30% of American veterans deployed to the 1990-91 Persian Gulf War and is characterized by cognitive post-exertional malaise following physical effort. Gulf War Illness remains controversial since cognitive post-exertional malaise is also present in the more common Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. An objective dissociation between neural substrates for cognitive post-exertional malaise in Gulf War Illness and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome would represent a biological basis for diagnostically distinguishing these two illnesses. Here, we used functional magnetic resonance imaging to measure neural activity in healthy controls and patients with Gulf War Illness and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome during an N-back working memory task both before and after exercise. Whole brain activation during working memory (2-Back > 0-Back) was equal between groups prior to exercise. Exercise had no effect on neural activity in healthy controls yet caused deactivation within dorsal midbrain and cerebellar vermis in Gulf War Illness relative to Myalgic Encephalomyelitis/Chronic Fatigue Syndrome patients. Further, exercise caused increased activation among Myalgic Encephalomyelitis/Chronic Fatigue Syndrome patients within the dorsal midbrain, left operculo-insular cortex (Rolandic operculum) and right middle insula. These regions-of-interest underlie threat assessment, pain, interoception, negative emotion and vigilant attention. As they only emerge post-exercise, these regional differences likely represent neural substrates of cognitive post-exertional malaise useful for developing distinct diagnostic criteria for Gulf War Illness and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.

[Exploring the Role of Chemokine Receptor 6 \(*Ccr6*\) in the BXD Mouse Model of Gulf War Illness](#)

Front Neurosci. 2020 Aug 14;14:818. doi: 10.3389/fnins.2020.00818.eCollection 2020.

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- PMID: [32922257](#)
- PMCID: [PMC7456958](#)
- DOI: [10.3389/fnins.2020.00818](#)

Abstract

Gulf War illness (GWI) is a chronic and multi-symptomatic disorder with persistent neuroimmune symptomatology. Chemokine receptor 6 (CCR6) has been shown to be involved in several inflammation disorders in humans. However, the causative relationship between *CCR6* and neuroinflammation in GWI has not yet been investigated. By using RNA-seq data of prefrontal cortex (PFC) from 31 C57BL/6J X DBA/2J (BXD) recombinant inbred (RI) mouse strains and their parental strains under three chemical treatment groups - saline control (CTL), diisopropylfluorophosphate (DFP), and corticosterone combined with diisopropylfluorophosphate (CORT+DFP), we identified *Ccr6* as a candidate gene underlying individual differences in susceptibility to GWI. The *Ccr6* gene is *cis*-regulated and its expression is significantly correlated with CORT+DFP treatment. Its mean transcript abundance in PFC of BXD mice decreased 1.6-fold ($p < 0.0001$) in the CORT+DFP group. The response of *Ccr6* to CORT+DFP is also significantly different ($p < 0.0001$) between the parental strains, suggesting *Ccr6* is affected by both host genetic background and chemical treatments. Pearson product-moment correlation analysis revealed 1473 *Ccr6*-correlated genes ($p < 0.05$). Enrichment of these genes was seen in the immune, inflammation, cytokine, and neurological related categories. In addition, we also found five central nervous system-related phenotypes and fecal corticosterone concentration have significant correlation ($p < 0.05$) with expression of *Ccr6* in the PFC. We further established a protein-protein interaction subnetwork for the *Ccr6*-correlated genes, which provides an insight on the interaction of G protein-coupled receptors, kallikrein-kinin system and neuroactive ligand-receptors. This analysis likely defines the heterogeneity and complexity of GWI. Therefore, our results suggest that *Ccr6* is one of promising GWI biomarkers.

[Changes in Health Status in the Ft. Devens Gulf War Veterans Cohort: 1997-2017](#)

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- PMID: [32914090](#)
- PMCID: [PMC7444112](#)
- DOI: [10.1177/2633105520952675](#)

Abstract

Gulf War veterans (GWVs) were exposed to numerous neurotoxicants during deployment. Upon returning home, many reported a multitude of symptoms including fatigue, pain, gastrointestinal and respiratory issues, and neurological, cognitive, and mood complaints, collectively termed "Gulf War Illness (GWI)." Now, nearly 30 years post-war, many GWVs continue to suffer from these symptoms, in addition to health concerns associated with normal aging. While most research on GWVs has been cross-sectional, it is important to evaluate the progression and onset of new GWI symptoms longitudinally. The current study investigated the health of GWVs 25+ years after the war by resurveying the Ft. Devens Cohort and comparing their current health to their health reported 15 to 20 years earlier. The sample consists of 317 GWVs (~54 years old at the latest survey, 38 women) who responded to both surveys (1997-1998 and 2013-2017). Multivariable regression analyses were used to assess changes in GWI symptomatology and prevalence of medical conditions. The rates of 12 of 25 health symptoms increased significantly from the prior 1997-1998 survey. Anxiety, numbness in extremities, depressed mood, and joint pain had the greatest increase in endorsement. The rates of 7 of 16 medical conditions increased significantly from the prior 1997-1998 survey. High blood pressure, diabetes, and cancer had the greatest increase in prevalence. In summary, this study demonstrates that both symptoms and physician-diagnosed medical conditions associated with GW deployment/exposure increased in prevalence. For GWVs, focus by providers on the treatment of cognitive and mental health issues as well as cardiovascular and cerebrovascular risk factors is warranted. Targeting symptom alleviation would help improve the quality of life in these veterans until treatments addressing the entire illness become available.

The Low Glutamate Diet Effectively Improves Pain and Other Symptoms of Gulf War Illness

Nutrients. 2020 Aug 26;12(9):E2593. doi: 10.3390/nu12092593.

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Abstract

Gulf War Illness (GWI) is a multisymptom disorder including widespread chronic pain, fatigue and gastrointestinal problems. The objective of this study was to examine the low glutamate diet as a treatment for GWI. Forty veterans with GWI were recruited from across the US. Outcomes included symptom score, myalgic score, tender point count, dolorimetry and the Chalder Fatigue Scale. Subjects were randomized to the low glutamate diet or a wait-listed control group, with symptom score being compared after one month. Subjects then went onto a double-blind, placebo-controlled crossover challenge with monosodium glutamate (MSG)/placebo to test for return of symptoms. Symptom score was compared between diet intervention and wait-listed controls with an independent t-test and effect size was calculated with Cohen's *d*. Change scores were analyzed with Wilcoxon Signed Rank tests. Crossover challenge results were analyzed with General Linear Models and cluster analysis. The diet intervention group reported significantly less symptoms ($p = 0.0009$) than wait-listed controls, with a very large effect size, $d = 1.16$. Significant improvements in average dolorimetry ($p = 0.0006$), symptom score, tender point number, myalgic score and the Chalder Fatigue Scale (all $p < 0.0001$) were observed after the 1-month diet. Challenge with MSG/placebo resulted in significant variability in individual response. These results suggest that the low glutamate diet can effectively reduce overall symptoms, pain and fatigue in GWI, but differential results upon challenge suggest that other aspects of the diet, or underlying differences within the population, may be driving these changes. Future research is needed to identify potential nutrient effects, biomarkers, and underlying metabolic differences between responders and non-responders.

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An analysis of 2-day cardiopulmonary exercise testing to assess unexplained fatigue

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Abstract

Two consecutive maximal cardiopulmonary exercise tests (CPETs) performed 24 hr apart (2-day CPET protocol) are increasingly used to evaluate post-exertional malaise (PEM) and related disability among individuals with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). This protocol may extend to other fatiguing illnesses with similar characteristics to ME/CFS; however, 2-day CPET protocol reliability and minimum change required to be considered clinically meaningful (i.e., exceeding the standard error of the measure) are not well characterized. To address this gap, we evaluated the 2-day CPET protocol in Gulf War Illness (GWI) by quantifying repeatability of seven CPET parameters, establishing their thresholds of clinically significant change, and determining whether changes differed between veterans with GWI and controls. Excluding those not attaining peak effort criteria ($n = 15$), we calculated intraclass correlation coefficients (ICCs), the smallest real difference (SRD%), and repeated measures analysis of variance (RM-ANOVA) at the ventilatory anaerobic threshold (VAT) and peak exercise in 15 veterans with GWI and eight controls. ICC values at peak ranged from moderate to excellent for veterans with GWI (mean [range]; 0.84 [0.65 - 0.92]) and were reduced at the VAT (0.68 [0.37 - 0.78]). Across CPET variables, the SRD% at peak exercise for veterans with GWI (18.8 [8.8 - 28.8]) was generally lower than at the VAT (28.1 [9.5 - 34.8]). RMANOVAs did not detect any significant group-by-time interactions (all $p > .05$). The methods and findings reported here provide a framework for evaluating 2-day CPET reliability, and reinforce the importance of carefully considering measurement error in the population of interest when interpreting findings.

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Development of muscle atrophy and loss of function in a Gulf-War illness model: underlying mechanisms

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Abstract

Gulf War illness (GWI) afflicts military personnel who served during the Persian Gulf War and is notable for cognitive deficits, depression, muscle pain, weakness, intolerance to exercise, and fatigue. Suspect causal agents include the chemicals pyridostigmine (PB), permethrin (PM) and N,N-diethyl-m-toluamide (DEET) used as protectants against insects and nerve gases. No pre-clinical studies have explored the effects on skeletal muscle (SkM). Young male rats were provided PB, PM and DEET at equivalent human doses and physical restraint (to induce stress) for 3 weeks followed a 3-week recovery. GWI gastrocnemius weight was ~ 35% lower versus controls, which correlated with decreases in myofiber area, limb strength, and treadmill time/distance. In GWI rats, SkM fiber type relative abundance changed towards slow type I. Muscle wasting pathway proteins were upregulated while those that promote growth decreased as did mitochondrial endpoints and muscle ATP levels. Proteomic analysis of SkM also documented unique alterations in mitochondrial and metabolic pathways. Thus, exposure to GWI chemicals/stress adversely impacts key metabolic pathways leading to muscle atrophy and loss of function. These changes may account for GWI Veterans symptoms.

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Using Plasma Autoantibodies of Central Nervous System Proteins to Distinguish Veterans with Gulf War Illness from Healthy and Symptomatic Controls

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Abstract

For the past 30 years, there has been a lack of objective tools for diagnosing Gulf War Illness (GWI), which is largely characterized by central nervous system (CNS) symptoms emerging from 1991 Gulf War (GW) veterans. In a recent preliminary study, we reported the presence of autoantibodies against CNS proteins in the blood of veterans with GWI, suggesting a potential objective biomarker for the disorder. Now, we report the results of a larger, confirmatory study of these objective biomarkers in 171 veterans with GWI compared to 60 healthy GW veteran controls and 85 symptomatic civilian controls ($n = 50$ myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and $n = 35$ irritable bowel syndrome (IBS)). Specifically, we compared plasma markers of CNS autoantibodies for diagnostic characteristics of the four groups (GWI, GW controls, ME/CFS, IBS). For veterans with GWI, the results showed statistically increased levels of nine of the ten autoantibodies against neuronal "tubulin, neurofilament protein (NFP), Microtubule Associated Protein-2 (MAP-2), Microtubule Associated Protein-Tau (Tau), alpha synuclein (α -syn), calcium calmodulin kinase II (CaMKII)" and glial proteins "Glial Fibrillary Acidic Protein (GFAP), Myelin Associated Glycoprotein (MAG), Myelin Basic Protein (MBP), S100B" compared to healthy GW controls as well as civilians with ME/CFS and IBS. Next, we summed all of the means of the CNS autoantibodies for each group into a new index score called the Neurodegeneration Index (NDI). The NDI was calculated for each tested group and showed veterans with GWI had statistically significantly higher NDI values than all three control groups. The present study confirmed the utility of the use of plasma autoantibodies for CNS proteins to distinguish among veterans with GWI and other healthy and symptomatic control groups.

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Obesity Worsens Gulf War Illness Symptom Persistence Pathology by Linking Altered Gut Microbiome Species to Long-Term Gastrointestinal, Hepatic, and Neuronal Inflammation in a Mouse Model

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Abstract

Persistence of Gulf War illness (GWI) pathology among deployed veterans is a clinical challenge even after almost three decades. Recent studies show a higher prevalence of obesity and metabolic disturbances among Gulf War veterans primarily due to the existence of post-traumatic stress disorder (PTSD), chronic fatigue, sedentary lifestyle, and consumption of a high-carbohydrate/high-fat diet. We test the hypothesis that obesity from a Western-style diet alters host gut microbial species and worsens gastrointestinal and neuroinflammatory symptom persistence. We used a 5 month Western diet feeding in mice that received prior Gulf War (GW) chemical exposure to mimic the home phase obese phenotype of the deployed GW veterans. The host microbial profile in the Western diet-fed GWI mice showed a significant decrease in butyrogenic and immune health-restoring bacteria. The altered microbiome was associated with increased levels of IL6 in the serum, Claudin-2, IL6, and IL1 β in the distal intestine with concurrent inflammatory lesions in the liver and hyperinsulinemia. Microbial dysbiosis was also associated with frontal cortex levels of increased IL6 and IL1 β , activated microglia, decreased levels of brain derived neurotrophic factor (BDNF), and higher accumulation of phosphorylated Tau, an indicator of neuroinflammation-led increased risk of cognitive deficiencies. Mechanistically, serum from Western diet-fed mice with GWI significantly increased microglial activation in transformed microglial cells, increased tyrosyl radicals, and secreted IL6. Collectively, the results suggest that an existing obese phenotype in GWI worsens persistent gastrointestinal and neuronal inflammation, which may contribute to poor outcomes in restoring cognitive function and resolving fatigue, leading to the deterioration of quality of life.

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Assessing the Beneficial Effects of the Immunomodulatory Glycan LNFPIII on Gut Microbiota and Health in a Mouse Model of Gulf War Illness

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Abstract

The microbiota's influence on host (patho) physiology has gained interest in the context of Gulf War Illness (GWI), a chronic disorder featuring dysregulation of the gut-brain-immune axis. This study examined short- and long-term effects of GWI-related chemicals on gut health and fecal microbiota and the potential benefits of Lacto-N-fucopentaose-III (LNFPIII) treatment in a GWI model. Male C57BL/6J mice were administered pyridostigmine bromide (PB; 0.7 mg/kg) and permethrin (PM; 200 mg/kg) for 10 days with concurrent LNFPIII treatment (35 µg/mouse) in a short-term study (12 days total) and delayed LNFPIII treatment (2×/week) beginning 4 months after 10 days of PB/PM exposure in a long-term study (9 months total). Fecal 16S rRNA sequencing was performed on all samples post-LNFPIII treatment to assess microbiota effects of GWI chemicals and acute/delayed LNFPIII administration. Although PB/PM did not affect species composition on a global scale, it affected specific taxa in both short- and long-term settings. PB/PM elicited more prominent long-term effects, notably, on the abundances of bacteria belonging to *Lachnospiraceae* and *Ruminococcaceae* families and the genus *Allobaculum*. LNFPIII improved a marker of gut health (i.e., decreased lipocalin-2) independent of GWI and, importantly, increased butyrate producers (e.g., *Butyricoccus*, *Ruminococcus*) in PB/PM-treated mice, indicating a positive selection pressure for these bacteria. Multiple operational taxonomic units correlated with aberrant behavior and lipocalin-2 in PB/PM samples; LNFPIII was modulatory. Overall, significant and lasting GWI effects occurred on specific microbiota and LNFPIII treatment was beneficial.

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Radiation Exposure Predicts Reported Vaccine Adverse Effects in Veterans with Gulf War Illness

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Abstract

Most people have no problems when administered vaccines; however, as with all drugs, reported adverse effects (rAEs) do occur. There is a need to better understand the potential predictors of reported vaccine AEs (rVaxAEs), including modifiable (environmental) predictors. Gulf War Veterans (GWV) who have Gulf War illness (GWI) report increased experiences of drug and chemical rAEs, extending to rVaxAEs. GWV provide an opportunity to examine the relationship between their reported exposures and rAEs. Forty one GWV with GWI and 40 healthy controls reported exposure and rAEs to exposure, including for 14 vaccines. Individual and summed vaccine exposures, rVaxAEs, and reported Vaccine AE Propensity (summed rVaxAEs/summed vaccines exposures) were compared in cases vs. controls. Exposure-outcome assessments focused on GWV, using a multivariable regression with robust standard error. More designated vaccines were reported in cases than in controls: 9.0 (2.3) vs. 3.8 (2.3), $p < 0.0001$. The fraction of vaccines received that led to rAEs was ten-fold higher in cases: 0.24 (0.21), vs. 0.023 (0.081), $p < 0.0001$. Multivariable assessment confirmed that radiation and pesticides remained significant statistical predictors of reported Vaccine AE Propensity. Exposure tied to excess rVaxAEs in GWV may contribute to, or underlie, the reported link between rVaxAEs in GWV and later ill health.

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The Prevalence of Mild Cognitive Impairment in a Convenience Sample of 202 Gulf War Veterans

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Abstract

Gulf War Illness (GWI) is a chronic, multisymptom disorder estimated to affect approximately 25-32% of Gulf War veterans (GWVs). Cognitive dysfunction is a common symptom of GWI. On the continuum of cognitive decline, mild cognitive impairment (MCI) is conceptualized as a transitional phase between normal aging and dementia. Individuals with MCI exhibit cognitive decline but have relatively spared activities of daily function and do not meet criteria for dementia. The current study sought to investigate the prevalence of MCI in a convenience sample of 202 GWVs (median age: 52 years; 18% female). Twelve percent of the sample (median age: 48 years) had MCI according to an actuarial neuropsychological criterion, a rate materially higher than expected for this age group. GWVs with MCI also had a smaller hippocampal volume and a thinner parietal cortex, higher rates of current posttraumatic stress disorder and major depressive disorder compared to GWVs without MCI. Because people with MCI are more likely to progress to dementia compared to those with normal cognition, these results may portend future higher rates of dementia among deployed GWVs.

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