Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI) — PubMed Research Citations for July, Aug, Sept 2021

Prepared by Staff of the RACGWVI.

RACGWVI: Gulf War Illness — PubMed Citations for July, Aug, Sept 2021

The following is a list of published research projects that focus on Gulf War Illness (GWI) for the months of July, August and September 2021.

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Melatonin improves brain function in a model of chronic Gulf War Illness with modulation of oxidative stress, NLRP3 inflammasomes, and BDNF-ERK-CREB pathway in the hippocampus

Redox Biol. 2021 Jul; 43:101973. doi: 10.1016/j.redox.2021.101973. Epub 2021 Apr 22.

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Abstract

Persistent cognitive and mood dysfunction is the primary CNS symptom in veterans afflicted with Gulf War Illness (GWI). This study investigated the efficacy of melatonin (MEL) for improving cognitive and mood function with antioxidant, antiinflammatory, and pro-cognitive effects in a rat model of chronic GWI. Six months after exposure to GWI-related chemicals and stress, rats were treated with vehicle or MEL (5, 10, 20, 40, and 80 mg/kg) for eight weeks. Behavioral tests revealed cognitive and mood dysfunction in GWI rats receiving vehicle, which were associated with elevated oxidative stress, reduced NRF2, catalase and mitochondrial complex proteins, astrocyte hypertrophy, activated microglia with NLRP3 inflammasomes, elevated proinflammatory cytokines, waned neurogenesis, and synapse loss in the hippocampus. MEL at 10 mg/kg alleviated simple and associative recognition memory dysfunction and anhedonia, along with reduced oxidative stress, enhanced glutathione and complex III, and reduced NLRP3 inflammasomes, IL-18, TNF-α, and IFN-γ. MEL at 20 mg/kg also normalized NRF2 and catalase and increased microglial ramification. MEL at 40 mg/kg, in addition, reduced astrocyte hypertrophy, activated microglia, NF-kB-NLRP3-caspase-1 signaling, IL-1β, MCP-1, and MIP-1α. Moreover, MEL at 80 mg/kg activated the BDNF-ERK-CREB signaling pathway, enhanced neurogenesis and diminished synapse loss in the hippocampus, and improved a more complex hippocampus-dependent cognitive function. Thus, MEL therapy is efficacious for improving cognitive and mood function in a rat model of chronic GWI, and MEL's effect was dose-dependent. The study provides the first evidence of MEL's promise for alleviating neuroinflammation and cognitive and mood impairments in veterans with chronic GWI.

Keywords: Brain-derived neurotrophic factor; Cognitive and mood function; Inflammasomes; Mitochondria; Neurogenesis; Neuroinflammation; Oxidative stress; cAMP response element-binding protein.

Heart rate and heart rate variability as outcomes and longitudinal moderators of treatment for pain across follow-up in Veterans with Gulf War illness

Life Sci. 2021 Jul 15; 277:119604. doi: 10.1016/j.lfs.2021.119604. Epub 2021 May 11.

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Abstract

Aims: Accumulating evidence suggests Gulf War illness (GWI) is characterised by autonomic nervous system dysfunction (higher heart rate [HR], lower heart rate variability [HRV]). Yoga - an ancient mind-body practice combining mindfulness, breathwork, and physical postures - is proposed to improve autonomic dysfunction yet this remains untested in GWI. We aimed to determine (i) whether HR and HRV improve among Veterans with GWI receiving either yoga or cognitive behavioural therapy (CBT) for pain; and (ii) whether baseline autonomic functioning predicts treatment-related pain outcomes across follow-up.

Main methods: We present secondary analyses of 24-hour ambulatory cardiac data (mean HR, square root of the mean squared differences between successive R-R intervals [RMSSD], high frequency power [HF-HFV], and low-to-high frequency ratio [LF/HF] extracted from a 5-min window during the first hour of sleep) from our randomised controlled trial of yoga versus CBT for pain among Veterans with GWI (ClinicalTrials.govNCT02378025; N = 75).

Key findings: Veterans who received CBT tended towards higher mean HR at end-of-treatment. Better autonomic function (lower mean HR, higher RMSSD/HF-HRV) at baseline predicted greater reductions in pain across follow-up, regardless of treatment group. Better baseline autonomic function (mid-range-to-high RMSSD/HF-HRV) also predicted greater pain reductions with yoga, while worse baseline autonomic function (higher mean HR, lower RMSSD/HF-HRV) predicted greater pain reductions with CBT.

Significance: To our knowledge, this is the first study to suggest that among Veterans with GWI, HR may increase with CBT yet remain stable with yoga. Furthermore, HR and HRV moderated pain outcome across follow-up for yoga and CBT.

Minocycline alleviates Gulf War Illness rats via altering gut microbiome, attenuating neuroinflammation and enhancing hippocampal neurogenesis

Behav Brain Res. 2021 Jul 23; 410:113366. doi: 10.1016/j.bbr.2021.113366. Epub 2021 May 14.

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Abstract

Accumulating evidences suggest that deficits in neurogenesis, chronic inflammation and gut microbiome dysregulation contribute to the pathophysiology of Gulf War Illness (GWI). Minocycline has been demonstrated to be a potent neuroprotective agent and could regulate neuroinflammation. The present study intends to investigate whether the treatment of minocycline maintains better cognition and mood function in a rat model of GWI and the potential mechanism. Rats received 28 days of GWI-related chemical exposure and restraint stress, along with daily minocycline or vehicle treatment. Cognitive and mood function, neuroinflammation, neurogenesis and gut microbiota were detected. We found that minocycline treatment induces better cognitive and mood function in the GWI rat model, as indicated by open-field test, elevated plus maze test, novel object recognition test and forced swim test. Moreover, minocycline treatment reversed the altered gut microbiome, neuroinflammation and the decreased hippocampal neurogenesis of rats with GWI. Taken together, our study indicated that minocycline treatment exerts better cognitive and mood function in GWI rat model, which is possibly related to gut microbiota remodeling, restrained inflammation and enhanced hippocampal neurogenesis. These results may establish minocycline as a potential prophylactic or therapeutic agent for the treatment of GWI.

Andrographolide Attenuates Gut-Brain-Axis Associated Pathology in Gulf War Illness by Modulating Bacteriome-Virome Associated Inflammation and Microglia-Neuron Proinflammatory Crosstalk

Brain Sci. 2021 Jul 9; 11(7):905. doi: 10.3390/brainsci11070905.

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Abstract

Gulf War Illness (GWI) is a chronic multi-symptomatic illness that is associated with fatigue, pain, cognitive deficits, and gastrointestinal disturbances and presents a significant challenge to treat in clinics. Our previous studies show a role of an altered Gut-Brain axis pathology in disease development and symptom persistence in GWI. The present study utilizes a mouse model of GWI to study the role of a labdane diterpenoid andrographolide (AG) to attenuate the Gut-Brain axis-linked pathology. Results showed that AG treatment in mice (100 mg/kg) via oral gavage restored bacteriome alterations, significantly increased probiotic bacteria *Akkermansia*, *Lachnospiraceae*, and *Bifidobacterium*, the genera that are known to aid in preserving gut and immune health. AG also corrected an altered virome with significant decreases in virome families *Siphoviridae* and *Myoviridae* known to be associated with gastrointestinal pathology. AG treatment significantly restored tight junction proteins that correlated well with decreased intestinal proinflammatory mediators IL-1β and IL-6 release. AG treatment could restore Claudin-5 levels, crucial for maintaining the BBB integrity. Notably, AG could decrease microglial activation and increase neurotrophic factor BDNF, the key to neurogenesis. Mechanistically, microglial conditioned medium generated from IL-6 stimulation with or without AG in a concentration similar to circulating levels found in the GWI mouse model and co-incubated with neuronal cells in vitro, decreased Tau phosphorylation and neuronal apoptosis. In conclusion, we show that AG treatment mitigated the Gut-Brain-Axis associated pathology in GWI and may be considered as a potential therapeutic avenue for the much-needed bench to bedside strategies in GWI.

Neuroimmune mechanisms of cognitive impairment in a mouse model of Gulf War illness

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Abstract

Gulf War Illness (GWI) is a chronic, multi-symptom disorder affecting approximately 30 percent of the nearly 700,000 Veterans of the 1991 Persian Gulf War. GWI-related chemical (GWIC) exposure promotes immune activation that correlates with cognitive impairment and other symptoms of GWI. However, the molecular mechanisms and signaling pathways linking GWIC to inflammation and neurological symptoms remain unclear. Here we show that acute exposure of murine macrophages to GWIC potentiates innate immune signaling and inflammatory cytokine production. Using an established mouse model of GWI, we report that neurobehavioral changes and neuroinflammation are attenuated in mice lacking the cyclic GMP-AMP synthase (cGAS)-Stimulator of Interferon Genes (STING) and NOD-, LRR- or pyrin domain-containing protein 3 (NLRP3) innate immune pathways. In addition, we report sex differences in response to GWIC, with female mice showing more pronounced cognitive impairment and hippocampal astrocyte hypertrophy. In contrast, male mice display a GWIC-dependent upregulation of proinflammatory cytokines in the plasma that is not present in female mice. Our results indicate that STING and NLRP3 are key mediators of the cognitive impairment and inflammation observed in GWI and provide important new information on sex differences in this model.

Experiential avoidance is associated with medical and mental health diagnoses in a national sample of deployed Gulf War veterans

J Psychiatr Res. 2021 Jul 22; 142:17-24. doi: 10.1016/j.jpsychires.2021.07.033. Online ahead of print.

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Abstract

A substantial minority of deployed Gulf War veterans developed posttraumatic stress disorder (PTSD), depression, and several chronic illnesses. Although military combat and exposure to certain nuclear, biological, and chemical agents (NBCs) increase risk for post-deployment health problems, they do not fully explain many Gulf War veteran health diagnoses and are not viable treatment targets. Experiential avoidance (EA; one's unwillingness to remain in contact with unpleasant internal experiences) is a modifiable psychosocial risk factor associated with PTSD and depression in veterans as well as pain and gastrointestinal diseases in the general population. In this study, we recruited a national sample of deployed Gulf War veterans (N = 454) to test the hypothesis that greater EA would be significantly associated with higher lifetime odds of PTSD,

depression, "Gulf War Illness" (GWI/CMI), and other chronic illnesses common in this veteran cohort. Participants completed a self-report battery assessing demographic, military-related, and health-related information. Multivariate analyses showed that after adjusting for age, sex, race, combat exposure, and NBC exposure, worse EA was associated with higher lifetime odds of PTSD, depression GWI/CMI, gastrointestinal problems, irritable bowel syndrome, arthritis, fibromyalgia, and chronic fatigue syndrome (ORs ranged 1.25 to 2.89; effect sizes ranged small to large), but not asthma or chronic obstructive pulmonary disease. Our findings suggest medical and mental health providers alike should assess for EA and potentially target EA as part of a comprehensive, biopsychosocial approach to improving Gulf War veterans' health and wellbeing. Study limitations and future research directions are also discussed.

Differential phosphoprotein signaling in the cortex in mouse models of Gulf War Illness using corticosterone and acetylcholinesterase inhibitors

Heliyon. 2021 Jul 12;7(7): e07552. doi: 10.1016/j.heliyon.2021.e07552. eCollection 2021 Jul.

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Abstract

Aims: Veterans from the 1990-91 Gulf War were exposed to acetylcholinesterase inhibitors (AChEIs), and, following service, an estimated one-third began suffering from a medically unexplained, multi-symptom illness termed Gulf War Illness (GWI). Previous research has developed validated rodent models that include exposure to exogenous corticosterone (CORT) and AChEIs to simulate high stress and chemical exposures encountered in theater. This combination of exposures in mice resulted in a marked increase in neuroinflammation, which is a common symptom of veterans suffering from GWI. To further elucidate the mechanisms associated with these mouse models of GWI, an investigation into intracellular responses in the cortex were performed to characterize the early cellular signaling changes associated with this exposure-initiated neuroinflammation.

Main methods: Adult male C57BL/6J mice were exposed to CORT in the drinking water (200 μg/mL) for 7 days followed by a single intraperitoneal injection of diisopropyl fluorophosphate (DFP; 4.0 mg/kg) or chlorpyrifos oxon (CPO; 8.0 mg/kg), on day 8 and euthanized 0.5, 2, and 24 h post-injection. Eleven post-translationally modified protein targets were measured using a multiplexed ELISA.

Key findings: Phosphoprotein responses were found to be exposure specific following AChEI insult, with and without CORT. Specifically, CORT + CPO exposure was found to sequentially activate several phosphoproteins involved in mitogen activated protein kinase signaling (p-MEK1/2, p-ERK1/2, and p-JNK). DFP alone similarly increased proteins in this pathway (p-RPS6, and p-JNK), but the addition of CORT ameliorated these affects.

Significance: The results of this study provide insight into differentially activated pathways depending on AChEI in these GWI models.

Acute gene expression changes in the mouse hippocampus following a combined Gulf War toxicant exposure

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Abstract

Aims: Approximately 30% of the nearly 700,000 Veterans who were deployed to the Gulf War from 1990 to 1991 have reported experiencing a variety of symptoms including difficulties with learning and memory, depression and anxiety, and increased incidence of neurodegenerative diseases. Combined toxicant exposure to acetylcholinesterase (AChE) inhibitors has been studied extensively as a likely risk factor. In this study, we modeled Gulf War exposure in male C57Bl/6J mice with simultaneous administration of three chemicals implicated as exposure hazards for Gulf War Veterans: pyridostigmine bromide, the anti-sarin prophylactic; chlorpyrifos, an organophosphate insecticide; and the repellant N,N-diethyl-m-toluamide (DEET).

Main methods: Following two weeks of daily exposure, we examined changes in gene expression by whole transcriptome sequencing (RNA-Seq) with hippocampal isolates. Hippocampal-associated spatial memory was assessed with a Y-maze task. We hypothesized that genes important for neuronal health become dysregulated by toxicant-induced damage and that these detrimental inflammatory gene expression profiles could lead to chronic neurodegeneration.

Key findings: We found dysregulation of genes indicating a pro-inflammatory response and downregulation of genes associated with neuronal health and several important immediate early genes (IEGs), including Arc and Egr1, which were both reduced approximately 1.5-fold. Mice exposed to PB + CPF + DEET displayed a 1.6-fold reduction in preference for the novel arm, indicating impaired spatial memory.

Significance: Differentially expressed genes observed at an acute timepoint may provide insight into the pathophysiology of Gulf War Illness and further explanations for chronic neurodegeneration after toxicant exposure.

The low glutamate diet improves cognitive functioning in veterans with Gulf War Illness and resting-state EEG potentially predicts response

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Abstract

Objectives: Gulf War Illness (GWI) is a chronic, multi-symptom disorder with underlying central nervous system dysfunction and cognitive impairments. The objective of this study was to test the low glutamate diet as a novel treatment for cognitive dysfunction among those with GWI, and to explore if baseline resting-state electroencephalography (EEG) could predict cognitive outcomes.

Methods: Cognitive functioning was assessed at baseline, after one-month on the diet, and across a two-week double-blind, placebo-controlled crossover challenge with monosodium glutamate (MSG) relative to placebo.

Results: Significant improvements were seen after one-month on the diet in overall cognitive functioning, and in all other domains tested (FDR $p < 0.05$), except for memory. Challenge with MSG resulted in significant inter-individual response variability ($p < 0.0001$). Participants were clustered according to baseline resting-state EEG using k-means clustering to explore the inter-individual response variability. Three distinct EEG clusters were observed, and each corresponded with differential cognitive effects during challenge with MSG: cluster 1 had cognitive benefit (24% of participants), cluster 2 had cognitive detriment (42% of participants), and cluster 3 had mild/mixed effects (33% of participants).

Discussion: These findings suggest that the low glutamate diet may be a beneficial treatment for cognitive impairment in GWI. Future research is needed to understand the extent to which resting-state EEG can predict response to the low glutamate diet and to explore the mechanisms behind the varied response to acute glutamate challenge.

Symptom attribution to a medically unexplained syndrome is associated with greater perceived severity and bothersomeness of symptoms in US military veterans

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Abstract

Objective: Medically unexplained symptoms (MUS) are prevalent among veteran and non-veteran populations. Current biopsychosocial theory implicates a multitude of factors in MUS development and perpetuation. The current study tests whether *physical symptom attribution* to MUS is associated with perceived symptom severity and bothersomeness and thereby might function to perpetuate MUS, as suggested by existing theory.

Design and main outcome measures: Military combat veterans (n = 243) answered postal-mail questions about their physical symptoms, severity of experienced symptoms, and attributions of these symptoms to MUS (e.g. Gulf War Illness) versus non-MUS conditions.

Results: Independent t-tests showed support for the first hypothesis-that those who experience the symptom and attribute it to MUS will perceive it to be more severe and bothersome than those who experience the symptom but do not attribute it to MUS. Paired-sample t-tests showed support for the second hypothesis-that experienced symptoms attributed to MUS by an individual will be perceived as more severe and bothersome than experienced symptoms the individual does not attribute to MUS.

Conclusions: Results highlight a potential role of symptom attribution in MUS perpetuation, through greater perceived severity and bothersomeness of MUS-attributed symptoms. Possible intervention targets may include behavior ramifications, such as coping strategies; more research is needed.

Delayed treatment with the immunotherapeutic LNFPIII ameliorates multiple neurological deficits in a pesticide-nerve agent prophylactic mouse model of Gulf War Illness

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Abstract

Residual effects of the 1990-1991 Gulf War (GW) still plague veterans 30 years later as Gulf War Illness (GWI). Thought to stem mostly from deployment-related chemical overexposures, GWI is a disease with multiple neurological symptoms with likely immunological underpinnings. Currently, GWI remains untreatable, and the long-term neurological disease manifestation is not characterized fully. The present study sought to expand and evaluate the long-term implications of prior GW chemicals exposure on neurological function 6-8 months post GWI-like symptomatology induction. Additionally, the beneficial effects of delayed treatment with the glycan immunotherapeutic lacto-N-fucopentaose III (LNFPIII) were evaluated. Male C57BL/6J mice underwent a 10-day combinational exposure (i.p.) to GW chemicals, the nerve agent prophylactic pyridostigmine bromide (PB) and the insecticide permethrin (PM; 0.7 and 200 mg/kg, respectively). Beginning 4 months after PB/PM exposure, a subset of the mice were treated twice a week until study completion with LNFPIII. Evaluation of cognition/memory, motor function, and mood was performed beginning 1 month after LNFPIII treatment initiation. Prior exposure to PB/PM produced multiple locomotor, neuromuscular, and sensorimotor deficits across several motor tests. Subtle anxiety-like behavior was also present in PB/PM mice in mood tests. Further, PB/PM-exposed mice learned at a slower rate, mostly during early phases of the learning and memory tests employed. LNFPIII treatment restored or improved many of these behaviors, particularly in motor and cognition/memory domains. Electrophysiology data collected from hippocampal slices 8 months post PB/PM exposure revealed modest aberrations in basal synaptic transmission and long-term potentiation in the dorsal or ventral hippocampus that were improved by LNFPIII treatment. Immunohistochemical analysis of tyrosine hydroxylase (TH), a dopaminergic marker, did not detect major PB/PM effects along the nigrostriatal pathway, but LNFPIII increased striatal TH. Additionally, neuroinflammatory cells were increased in PB/PM mice, an effect reduced by LNFPIII. Collectively, long-term neurobehavioral and neurobiological dysfunction associated with prior PB/PM exposure was characterized; delayed LNFPIII treatment provided multiple behavioral and biological beneficial effects in the context of GWI, highlighting its potential as a GWI therapeutic.

Circulating HMGB1 is elevated in veterans with Gulf War Illness and triggers the persistent pro-inflammatory microglia phenotype in male C57Bl/6J mice

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Abstract

Gulf War Illness (GWI) is a chronic, multi-symptom peripheral and CNS condition with persistent microglial dysregulation, but the mechanisms driving the continuous neuroimmune pathology are poorly understood. The alarmin HMGB1 is an autocrine and paracrine pro-inflammatory signal, but the role of circulating HMGB1 in persistent neuroinflammation and GWI remains largely unknown. Using the LPS model of the persistent microglial pro-inflammatory response, male C57Bl/6J mice injected with LPS (5 mg/kg IP) exhibited persistent changes in microglia morphology and elevated pro-inflammatory markers in the hippocampus, cortex, and midbrain 7 days after LPS injection, while the peripheral immune response had resolved. Ex vivo serum analysis revealed an augmented pro-inflammatory response to LPS when microglia cells were cultured with the 7-day LPS serum, indicating the presence of bioactive circulating factors that prime the microglial pro-inflammatory response. Elevated circulating HMGB1 levels were identified in the mouse serum 7 days after LPS administration and in the serum of veterans with GWI. Tail vein injection of rHMGB1 in male C57Bl/6 J mice elevated TNFα mRNA levels in the liver, hippocampus, and cortex, demonstrating HMGB1-induced peripheral and CNS effects. Microglia isolated at 7 days after LPS injection revealed a unique transcriptional profile of 17 genes when compared to the acute 3 H LPS response, 6 of which were also upregulated in the midbrain by rHMGB1, highlighting a distinct signature of the persistent pro-inflammatory microglia phenotype. These findings indicate that circulating HMGB1 is elevated in GWI, regulates the microglial neuroimmune response, and drives chronic neuroinflammation that persists long after the initial instigating peripheral stimulus.

Moderate, intermittent voluntary exercise in a model of Gulf War Illness improves cognitive and mood function with alleviation of activated microglia and astrocytes, and enhanced neurogenesis in the hippocampus

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Abstract

Persistent cognitive and mood impairments in Gulf War Illness (GWI) are associated with chronic neuroinflammation, typified by hypertrophied astrocytes, activated microglia, and increased proinflammatory mediators in the brain. Using a rat model, we investigated whether a simple lifestyle change such as moderate voluntary physical exercise would improve cognitive and mood function in GWI. Because veterans with GWI exhibit fatigue and post-exertional malaise, we employed an intermittent voluntary running exercise (RE) regimen, which prevented exercise-induced stress. The GWI rats were provided access to running wheels three days per week for 13 weeks, commencing ten weeks after the exposure to GWI-related chemicals and stress (GWI-RE group). Groups of age-matched sedentary GWI rats (GWI-SED group) and naïve rats were maintained parallelly. Interrogation of rats with behavioral tests after the 13-week RE regimen revealed improved hippocampus-dependent object location memory and pattern separation function and reduced anxiety-like behavior in the GWI-RE group compared to the GWI-SED group. Moreover, 13 weeks of RE in GWI rats significantly reversed activated microglia with short and less ramified processes into non-inflammatory/antiinflammatory microglia with highly ramified processes and reduced the hypertrophy of astrocytes. Moreover, the production of new neurons in the hippocampus was enhanced when examined eight weeks after the commencement of RE. Notably, increased neurogenesis continued even after the cessation of RE. Collectively, the results suggest that even a moderate, intermittent physical exercise has the promise to improve brain function in veterans with GWI in association with suppression of neuroinflammation and enhancement of hippocampal neurogenesis.

Changes in polyphenol serum levels and cognitive performance after dietary supplementation with Concord grape juice in veterans with Gulf War Illness

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Abstract

Aims: We investigated whether the consumption of Concord grape juice (CGJ) was associated with increased bioavailability of serum metabolites and their potential impact on cognitive performance in Veterans with Gulf War Illness (GWI).

Main methods: Twenty-six veterans were selected from a cohort of 36 enrolled in a 24-week randomized, double-blind, Phase I/IIA clinical trial exploring whether the consumption of Concord grape juice (CGJ) was tolerable and safe in Veterans with GWI and improved cognitive function and fatigue. These 26 veterans were selected based on their completion of the entire 24-week protocol and documented adherence to the study beverage ≥80%. Differences in serum metabolite levels between CGJ and placebo at midpoint and endpoint were evaluated using two-way repeated measures ANOVA with post hoc Sidak's multiple comparison test. Bivariate correlations to assess for possible relationships between change in serum metabolite levels and change in cognitive

function as measured by the Halstead Category Test-Russell Revised Version (RCAT) were also conducted.

Key findings: Seventy-six metabolites were identified and quantified in this study, with three (cyanidin-glucuronide, me-cyanidin-glucuronide, and me-malvidin-glucuronide) found to be significantly higher ($p < 0.05$) in the CGJ group compared to placebo at 24 weeks. Significant associations between changes in cognitive function and changes in serum levels of epicatechin-sulphate ($r = 0.48$, $p = 0.01$) and petunidin-glucuronide ($r = 0.53$, $p < 0.01$) from baseline to 24 weeks were also observed.

Significance: Our data suggest that dietary supplementation with CGJ is associated with increased bioavailability of specific phenolic metabolites, some of which may be correlated with cognitive performance.

Boston biorepository, recruitment and integrative network (BBRAIN): A resource for the Gulf War Illness scientific community

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Abstract

Aims: Gulf War Illness (GWI), a chronic debilitating disorder characterized by fatigue, joint pain, cognitive, gastrointestinal, respiratory, and skin problems, is currently diagnosed by self-reported symptoms. The Boston Biorepository, Recruitment, and Integrative Network (BBRAIN) is the collaborative effort of expert Gulf War Illness (GWI) researchers who are creating objective diagnostic and pathobiological markers and recommend common data elements for GWI research.

Main methods: BBRAIN is recruiting 300 GWI cases and 200 GW veteran controls for the prospective study. Key data and biological samples from prior GWI studies are being merged and combined into retrospective datasets. They will be made available for data mining by the BBRAIN network and the GWI research community. Prospective questionnaire data include general health and chronic symptoms, demographics, measures of pain, fatigue, medical conditions, deployment and exposure histories. Available repository biospecimens include blood, plasma, serum, saliva, stool, urine, human induced pluripotent stem cells and cerebrospinal fluid.

Key findings: To date, multiple datasets have been merged and combined from 15 participating study sites. These data and samples have been collated and an online request form for repository requests as well as recommended common data elements have been created. Data and biospecimen sample requests are reviewed by the BBRAIN steering committee members for approval as they are received.

Significance: The BBRAIN repository network serves as a much needed resource for GWI researchers to utilize for identification and validation of objective diagnostic and pathobiological markers of the illness.

A cohort study of neuropsychological functioning in spouses of U.S. Gulf War veterans

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Abstract

Aims: Veterans of the 1991 Gulf War reported symptoms in their spouses that mirrored veterans' symptoms following their return from the war, including problems with attention and memory. Neuropsychological functioning in these spouses has not been examined with objective tests. This study sought to determine if these spouses exhibited deficits in neuropsychological functioning.

Main methods: Spouses of a national cohort of 1991 Gulf War deployed (n = 470) and non-deployed veterans (n = 524) were examined with neuropsychological tests in 1999-2001.

Key findings: Neuropsychological tests were factor analyzed yielding five factors: verbal memory, visual memory, attention/working memory, visual organization, and motor speed. Spouses of deployed and nondeployed veterans did not differ on mean factor scores, percentage of impaired factors, or individual test scores. Spouse attention/working memory was related to their having diagnoses of PTSD or anxiety disorders, or self-reported symptoms of current anxiety. Spouse visual memory was related to a diagnosis of current depression. Spouse motor speed was related to their own status of having chronic multisymptom illness (CMI).

Significance: Spouses of Gulf War deployed and nondeployed veterans demonstrated similar neuropsychological functioning, although spouses with psychiatric diagnoses and symptoms, or CMI demonstrated neuropsychological impairments characteristic of those conditions, suggesting that monitoring spouses for these conditions and impairments may be warranted. This pattern of relative weaknesses mirrors some of the previously reported findings for Gulf War veterans, although the veterans displayed neuropsychological impairments beyond what was accounted for by these conditions.

Modeling Neuroimmune Interactions in Human Subjects and Animal Models to Predict Subtype-Specific Multidrug Treatments for Gulf War Illness

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Abstract

Gulf War Illness (GWI) is a persistent chronic neuroinflammatory illness exacerbated by external stressors and characterized by fatigue, musculoskeletal pain, cognitive, and neurological problems linked to underlying immunological dysfunction for which there is no known treatment. As the immune system and the brain communicate through several signaling pathways, including the hypothalamic-pituitary-adrenal (HPA) axis, it underlies many of the behavioral and physiological responses to stressors via blood-borne mediators, such as cytokines, chemokines, and hormones. Signaling by these molecules is mediated by the semipermeable blood-brain barrier (BBB) made up of a monocellular layer forming an integral part of the neuroimmune axis. BBB permeability can be altered and even diminished by both external factors (e.g., chemical agents) and internal conditions (e.g., acute or chronic stress, or cross-signaling from the hypothalamic-pituitary-gonadal (HPG) axis). Such a complex network of regulatory interactions that possess feed-forward and feedback connections can have multiple response dynamics that may include several stable homeostatic states beyond normal health. Here we compare immune and hormone measures in the blood of human clinical samples and mouse models of Gulf War Illness (GWI) subtyped by exposure to traumatic stress for subtyping this complex illness. We do this via constructing a detailed logic model of HPA-HPG-Immune regulatory behavior that also considers signaling pathways across the BBB to neuronal-glial interactions within the brain. We apply conditional interactions to model the effects of changes in BBB permeability. Several stable states are identified in the system beyond typical health. Following alignment of the human and mouse blood profiles in the context of the model, mouse brain sample measures were used to infer the neuroinflammatory state in human GWI and perform treatment simulations using a genetic algorithm to optimize the Monte Carlo simulations of the putative treatment strategies aimed at returning the ill system back to health. We identify several ideal multi-intervention strategies and potential drug candidates that may be used to treat chronic neuroinflammation in GWI.

Healthcare providers' perceived learning needs and barriers to providing care for chronic multisymptom illness and environmental exposure concerns

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Abstract

Objective: Patient provider encounters for chronic multisympom illness (CMI) and/or environmental exposures are difficult often resulting in Veterans and providers having high levels of dissatisfaction. Patients attribute these difficulties to providers lacking knowledge about these health concerns. It is not known whether providers perceive themselves as lacking expertise in CMI and environmental exposure concerns.

Methods: This needs assessment used a descriptive online survey design. A total of 3632 VA healthcare providers across disciplines were surveyed.

Results: Healthcare providers reported speaking with Veterans about CMI and environmental exposures despite feeling they have minimal to no knowledge of these topics. At the same time, only half of the providers had taken an available training on CMI or environmental exposure within the last year.

Conclusion: Healthcare providers recognize a knowledge gap regarding CMI and environmental exposures, despite this, there is low uptake of provider education on these topics.

Practice implications: A better understanding of barriers to uptake of training on CMI and environmental exposures is needed to increase engagement with these important trainings.

Lower blood malondialdehyde is associated with past pesticide exposure: findings in Gulf War illness and healthy controls

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Abstract

Background: Malondialdehyde (MDA) is a candidate general marker of oxidative stress (OS). We sought to assess the relation of MDA to Gulf War illness (GWI) and to a variety of exposures.

Methods: This is an observational study involving subjects from Southern California recruited from October 2011 to May 2014. MDA was assessed in 81 participants (41 GWI-cases, 40 controls). General and Gulf-specific exposures were elicited. MDA case-control comparison was restricted to 40 matched pairs. The potential association between MDA and exposures was assessed using regression analyses. Gulf-specific exposures were incorporated into a case-specific model.

Results: Plasma MDA was significantly lower in GWI-cases than controls. Composite pesticide and fuel-solvent exposures negatively predicted MDA in the total sample, as well as in the analyses that included either GWI-cases or controls only. Self-reported exposure to organophosphate (OP) nerve gas was a strong predictor for lower MDA level in veterans with GWI.

Conclusion: Past pesticide exposures predicted lower MDA in both veterans with GWI and in healthy controls.

Dysregulation of cellular energetics in Gulf War Illness

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Abstract

Gulf War Illness (GWI) is estimated to have affected about one third of the Veterans who participated in the first Persian Gulf War. The symptoms of GWI include chronic neurologic impairments, chronic fatigue syndrome, as well as fibromyalgia and immune system disorders, collectively referred to as chronic multi-symptom illness. Thirty years after the war, we still do not have an effective treatment for GWI. It is necessary to understand the molecular basis of the symptoms of GWI in order to develop appropriate therapeutic strategies. Cellular energetics are critical to the maintenance of cellular homeostasis, a process that is highly dependent on intact mitochondrial function and there is significant evidence from both human studies and animal models that mitochondrial impairments may lead to GWI symptoms. The available clinical and pre-clinical data suggest that agents that improve mitochondrial function have the potential to restore cellular energetics and treat GWI. To date, the experiments conducted in animal models of GWI have mainly focused on neurobehavioral aspects of the illness. Additional studies to address the fundamental biological processes that trigger the dysregulation of cellular energetics in GWI are warranted to better understand the underlying pathology and to develop new treatment methods. This review highlights studies related to mitochondrial dysfunction observed in both GW veterans and in animal models of GWI.

A common language for Gulf War Illness (GWI) research studies: GWI common data elements

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Abstract

Aims: The Gulf War Illness programs (GWI) of the United States Department of Veteran Affairs and the Department of Defense Congressionally Directed Medical Research Program collaborated with experts to develop Common Data Elements (CDEs) to standardize and systematically collect, analyze, and share data across the (GWI) research community.

Main methods: A collective working group of GWI advocates, Veterans, clinicians, and researchers convened to provide consensus on instruments, case report forms, and guidelines for GWI research. A similar initiative, supported by the National Institute of Neurologic Disorders and Stroke (NINDS) was completed for a comparative illness, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), and provided the foundation for this undertaking. The GWI working group divided into two sub-groups (symptoms and systems assessment). Both groups reviewed the applicability of instruments and forms recommended by the NINDS ME/CFS CDE to GWI research within specific domains and selected assessments of deployment exposures. The GWI CDE recommendations were finalized in March 2018 after soliciting public comments.

Key findings: GWI CDE recommendations are organized in 12 domains that include instruments, case report forms, and guidelines. Recommendations were categorized as core (essential), supplemental-highly recommended (essential for specified conditions, study types, or designs), supplemental (commonly collected, but not required), and exploratory (reasonable to use, but require further validation). Recommendations will continually be updated as GWI research progresses.

Significance: The GWI CDEs reflect the consensus recommendations of GWI research community stakeholders and will allow studies to standardize data collection, enhance data quality, and facilitate data sharing.

Lacto-N-fucopentaose-III ameliorates acute and persisting hippocampal synaptic plasticity and transmission deficits in a Gulf War Illness mouse model

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Abstract

Aims: The present study investigated if treatment with the immunotherapeutic, lacto-N-fucopentaose-III (LNFPIII), resulted in amelioration of acute and persisting deficits in synaptic plasticity and transmission as well as trophic factor expression along the hippocampal dorsoventral axis in a mouse model of Gulf War Illness (GWI).

Main methods: Mice received either coadministered or delayed LNFPIII treatment throughout or following, respectively, exposure to a 15-day GWI induction paradigm. Subsets of animals were subsequently sacrificed 48 h, seven months, or 11 months post GWI-related (GWIR) exposure for hippocampal qPCR or in vitro electrophysiology experiments.

Key findings: Progressively worsened impairments in hippocampal synaptic plasticity, as well as a biphasic effect on hippocampal synaptic transmission, were detected in GWIR-exposed animals. Dorsoventral-specific impairments in hippocampal synaptic responses became more pronounced over time, particularly in the dorsal hippocampus. Notably, delayed LNFPIII treatment ameliorated GWI-related aberrations in hippocampal synaptic plasticity and transmission seven and 11 months post-exposure, an effect that was consistent with enhanced hippocampal trophic factor expression and absence of increased interleukin 6 (IL-6) in animals treated with LNFPIII.

Significance: Approximately a third of Gulf War Veterans have GWI; however, GWI therapeutics are presently limited to targeted and symptomatic treatments. As increasing evidence underscores the substantial role of persisting neuroimmune dysfunction in GWI, efficacious neuroactive immunotherapeutics hold substantial promise in yielding GWI remission. The findings in the present report indicate that LNFPIII may be an efficacious candidate for ameliorating persisting neurological abnormalities presented in GWI.

Effects of gut microbiota remodeling on the dysbiosis induced by high fat diet in a mouse model of Gulf war illness

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Abstract

Gulf war illness (GWI) is a chronic disorder of unknown etiology characterized by multiple symptoms such as pain, fatigue, gastrointestinal disturbances and neurocognitive problems. Increasing evidence suggests that gut microbiome perturbations play a key role in the pathology of this disorder. GWI courses with gut microbiota alterations and their metabolites (e.g. short chain fatty acids -SCFA-), which can be aggravated by lifestyle risk factors such as a high fat diet (HF). To investigate the causative role of the gut microbiome, non-absorbable antibiotics (Abx) were administered to mice treated with GWI agents and concomitantly fed with a HF. In light of the wide use of Abx as pseudo-germ-free models, we evaluated the effects of Abx exposure on GWI and HF on body weight, food intake, gut microbiota changes and levels of the SCFA acetate. Results show that HF decreased food intake while increasing body weight in both controls and GWI. Exposure to Abx prevented these HF effects by offsetting the body weight gain in GWI. GWI and HF led to decreases in α-diversity, disruptions in the composition and structure of the gut bacterial community and decreases in acetate levels. This Abx-induced remodeling of the gut microbiome was characterized by an expansion of Proteobacteria, decreases in Bacteroidetes and Firmicutes, and overall increases in acetate levels, as well as by the proliferation of potential pathobionts. Therefore, the use of Abx may not represent a dependable approach to deplete the gut microbiome and its advantages as a pseudo germ-free model warrant further investigation.

Cognitive behavioral therapy for insomnia in veterans with gulf war illness: Results from a randomized controlled trial

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Abstract

Aims: To examine whether cognitive behavioral therapy for insomnia (CBT-I), delivered by telephone, improves sleep and non-sleep symptoms of Gulf War Illness (GWI).

Main methods: Eighty-five Gulf War veterans (21 women, mean age: 54 years, range 46-72 years) who met the Kansas GWI case definition, the Centers for Disease Control and Prevention (CDC) case definition for Chronic Multisymptom Illness (CMI), and research diagnostic criteria for insomnia disorder were randomly assigned to CBT-I or monitor-only wait list control. Eight weekly sessions of individual CBT-I were administered via telephone by Ph.D. level psychologists to study participants. Outcome measures included pre-, mid-, and post-treatment assessments of GWI and insomnia symptoms, subjective sleep quality, and continuous sleep monitoring with diary. Outcomes were re-assessed 6-months post-treatment in participants randomized to CBT-I.

Key findings: Compared to wait list, CBT-I produced significant improvements in overall GWI symptom severity, individual measures of fatigue, cognitive dysfunction, depression and anxiety, insomnia severity, subjective sleep quality, and sleep diary outcome measures. The beneficial effects of CBT-I on overall GWI symptom severity and most individual GWI symptom measures were maintained 6-months after treatment.

Significance: GWI symptoms have historically been difficult to treat. Because CBT-I, which is associated with low stigma and is increasingly readily available to veterans, improved both sleep and non-sleep symptoms of GWI, these results suggest that a comprehensive approach to the treatment of GWI should include behavioral sleep interventions.

Gulf War illness in the Gulf War Era Cohort and Biorepository: The Kansas and Centers for Disease Control definitions

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Abstract

Aims: This study characterizes Gulf War Illness (GWI) among U.S. veterans who participated in the Gulf War Era Cohort and Biorepository (GWECB).

Main methods: Mailed questionnaires were collected between 2014 and 2016. Self-reported GWI symptoms, symptom domain criteria, exclusionary diagnoses, and case status were examined based on the originally published Kansas and Centers for Disease Control (CDC) definitions in the GWECB cohort (n = 849 deployed to Gulf and n = 267 non-deployed). Associations among GWI and deployment status, demographic, and military service characteristics were examined using logistic regression.

Key findings: Among deployed veterans in our sample, 39.9% met the Kansas criteria and 84.2% met the CDC criteria for GWI. Relative to non-deployed veterans, deployed veterans had a higher odds of meeting four GWI case status-related measures including the Kansas symptom criteria (aOR = 2.05, 95% CI = 1.50, 2.80), Kansas GWI case status (aOR = 1.42, 95% CI = 1.05, 1.93), the CDC GWI case status (aOR = 1.57, 95% CI = 1.07, 2.29) and the CDC severe criteria (aOR = 2.67, 95% CI = 1.79, 3.99). Forty percent met the Kansas exclusionary criteria, with no difference by deployment status. Some symptoms were nearly universally endorsed.

Significance: This analysis provides evidence of a sustained, multisymptom illness in veterans who deployed to the Persian Gulf War compared to non-deployed Gulf War era veterans nearly 25

years later. Differences in symptoms attributed to GWI by deployment status have diminished since initial reports, suggesting the need to update GWI definitions to account for aging-related conditions and symptoms. This study provides a foundation for future efforts to establish a single GWI case definition and analyses that employ the biorepository.

Veterans with Gulf War Illness perceptions of management strategies

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Abstract

Aims: Gulf War Illness (GWI) is a prevalent and disabling condition characterized by persistent physical symptoms. Clinical practice guidelines recommend self-management to reduce the disability from GWI. This study evaluated which GWI self-management strategies patients currently utilize and view as most effective and ineffective.

Materials and methods: Data were collected from 267 Veterans during the baseline assessment of a randomized clinical trial for GWI. Respondents answered 3 open-ended questions regarding which self-management strategies they use, view as effective, and view as ineffective. Response themes were coded, and code frequencies were analyzed.

Key findings: Response frequencies varied across questions (in-use: n = 578; effective: n = 470; ineffective: n = 297). Healthcare use was the most commonly used management strategy (38.6% of 578), followed by lifestyle changes (28.5% of 578), positive coping (13% of 578), and avoidance (13.7% of 578). When asked about effective strategies, healthcare use (25.9% of 470), lifestyle change (35.7% of 470), and positive coping (17.4% of 470) were identified. Avoidance was frequently identified as ineffective (20.2% of 297 codes), as was invalidating experiences (14.1% of 297) and negative coping (10.4% of 297).

Significance: Patients with GWI use a variety of self-management strategies, many of which are consistent with clinical practice guidelines for treating GWI, including lifestyle change and non-pharmacological strategies. This suggests opportunities for providers to encourage effective self-management approaches that patients want to use.

Gulf War Illness Clinical Trials and Interventions Consortium (GWICTIC): A collaborative research infrastructure for intervention and implementation

Life Sci. 2021 Aug 1; 278:119636. doi: 10.1016/j.lfs.2021.119636. Epub 2021 May 17.

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Abstract

Aims: There is an inadequate portfolio of treatments for Gulf War Illness (GWI), a complex disease involving multiple organ systems, and early-phase clinical trials are hampered by many logistical problems. To address these challenges, the Gulf War Illness Clinical Trials and Interventions Consortium (GWICTIC) was formed with the aims of (i) creating a collaborative consortium of clinical and scientific researchers that will rapidly implement rigorous and innovative phase I and II clinical trials for GWI, (ii) perform at least four phase I or II clinical trials, (iii) provide a foundation of scalable infrastructure and management in support of the efficient and successful operation of the GWICTIC, and (iv) partner with the Boston Biorepository, Recruitment & Integrated Network for GWI and other GWI investigators to develop a common data element platform for core assessments and outcomes.

Main methods: The GWICTIC brings together a multidisciplinary team of researchers at several institutions to provide scientific innovation, statistical and computational rigor, and logistical efficiency in the development and implementation of early-phase low-risk clinical trials for GWI. The GWICTIC core trials adhere to a Veteran-centered philosophy and focus on interventions with multiple mechanistic targets to maximize the likelihood of efficacy. To support rapid and efficient study startup and implementation across the GWI research community, the GWICTIC will share infrastructure with investigator-initiated research studies funded under separate mechanisms.

Significance: The GWICTIC will leverage the efficiencies of centralized research support and innovative trial designs to address several longstanding needs in the GWI interventions research community.

Brain-Immune Interactions as the Basis of Gulf War Illness: Clinical Assessment and Deployment Profile of 1990-1991 Gulf War Veterans in the Gulf War Illness Consortium (GWIC) Multisite Case-Control Study

Brain Sci. 2021 Aug 26;11(9):1132. doi: 10.3390/brainsci11091132.

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Abstract

The Boston University-based Gulf War Illness Consortium (GWIC) is a multidisciplinary initiative developed to provide detailed understanding of brain and immune alterations that underlie Gulf War illness (GWI), the persistent multisymptom disorder associated with military service in the 1990-1991 Gulf War. The core GWIC case-control clinical study conducted in-depth brain and immune evaluation of 269 Gulf War veterans (223 GWI cases, 46 controls) at three U.S. sites that included clinical assessments, brain imaging, neuropsychological testing, and analyses of a broad range of immune and immunogenetic parameters. GWI cases were similar to controls on most demographic, military, and deployment characteristics although on average were two years younger, with a higher proportion of enlisted personnel vs. officers. Results of physical evaluation and routine clinical lab tests were largely normal, with few differences between GWI cases and healthy controls. However, veterans with GWI scored significantly worse than controls on standardized assessments of general health, pain, fatigue, and sleep quality and had higher rates of diagnosed conditions that included hypertension, respiratory and sinus conditions, gastrointestinal conditions, and current or lifetime depression and post-traumatic stress disorder. Among multiple deployment experiences/exposures reported by veterans, multivariable logistic regression identified just two significant GWI risk factors: extended use of skin pesticides in theater (adjusted OR = 3.25, $p = 0.005$) and experiencing mild traumatic brain injury during deployment (OR = 7.39, $p = 0.009$). Gulf War experiences associated with intense stress or trauma (e.g., participation in ground combat) were not associated with GWI. Data and samples from the GWIC project are now stored in a repository for use by GWI researchers. Future reports will present detailed findings on brain structure and function, immune function, and association of neuroimmune measures with characteristics of GWI and Gulf War service.

"Because the country, it seems though, has turned their back on me": Experiences of institutional betrayal among veterans living with Gulf War Illness

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Abstract

People living with medically unexplained symptoms (MUS) often have poor quality of life and health outcomes. Many struggle to engage with and trust in healthcare systems. This qualitative study examined how experiences with institutions influence perceptions of medical care for MUS by applying the theoretical framework of institutional betrayal to narratives of U.S. military Veterans living with Gulf War Illness (GWI). Institutional betrayal refers to situations in which the institutions people depend upon for safety and well-being cause them harm. Experiences of institutional betrayal both during active military service and when first seeking treatment appeared to shape perceptions of healthcare in this sample. Veterans expressed the belief that the military failed to protect them from environmental exposures. Veterans' concerns regarding subsequent quality of healthcare were intrinsically linked to a belief that, despite official documentation to the contrary, the predominant paradigm of both the U.S. Department of Defense and the U.S. Department of Veterans Affairs (VA) is that GWI does not exist. Veterans reported that providers are not adequately trained on treatment of GWI and do not believe Veterans' descriptions of their illness. Veterans reported taking up self-advocacy, doing their own research on their condition, and resigning themselves to decrease engagement with VA healthcare or seek non-VA care. The study's findings suggest institutional level factors have a profound impact on perceptions of care and the patient-provider relationship. Future research and policy aimed at improving healthcare for people living with MUS should consider the concept of institutional betrayal.

Epigenetic histone acetylation and Bdnf dysregulation in the hippocampus of rats exposed to repeated, low-dose diisopropylfluorophosphate

Life Sci. 2021 Sep 15; 281:119765. doi: 10.1016/j.lfs.2021.119765. Epub 2021 Jun 26.

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Abstract

Aims: Deployment-related exposures to organophosphate (OP) compounds are implicated for Gulf War Illness (GWI) development in First GW veterans. However, reasons for the persistence of GWI are not fully understood. Epigenetic modifications to chromatin are regulatory mechanisms that can adaptively or maladaptively respond to external stimuli. These include DNA methylation and histone acetylation. DNA methylation changes have been reported in GWI but the role of histone acetylation in GWI has been less explored, despite its importance as an epigenetic mechanism for neurological disorders.

Main methods: Male Sprague-Dawley rats were exposed to OP diisopropyl fluorophosphate (DFP, 0.5 mg/kg s.c., 5-d) and 6-m later brains were dissected for hippocampus. Western blotting, activity assays and chromatin immunoprecipitation (ChIP) were utilized for epigenetic analyses. Behavior was assessed using the Forced Swim Test (FST) and the Elevated Plus Maze (EPM).

Key findings: We observed a significant upregulation in HDAC1 protein along with a significant increase in HDAC enzyme activity in the hippocampus of DFP rats. A locus-specific ChIP study revealed decreases in H3K9ac at the brain derived neurotrophic factor (Bdnf) promoter IV coupled with a significant decrease in BDNF protein in DFP rat hippocampus. Treatment with HDAC inhibitor valproic acid reduced HDAC activity and decreased the FST immobility time in DFP rats.

Significance: Our research suggests that epigenetic alterations to histone acetylation pathways and decreased BDNF expression could represent novel mechanisms for GWI symptomatology and may provide new targets for developing effective drugs for GWI treatment.

Elevated somatic mutation and evidence of genomic instability in veterans with Gulf War illness

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Abstract

Aims: Gulf War illness (GWI) is thought to be associated with exposures experienced by soldiers deployed in the 1991 Gulf War. A major question is how these exposures continue to influence the health of these individuals three decades later. One potentially permanent effect of such exposures is the induction of genetic mutations. We investigated whether veterans with GWI exhibited persistently elevated levels of somatic mutation.

Materials and methods: We applied the blood-based glycophorin A (GPA) somatic mutation assay to a cohort of veterans diagnosed with GWI and a set of both concurrent and historic age-matched controls. This assay quantifies red blood cells with a phenotype consistent with loss of one allele at the genetic determinant for the MN blood group, the GPA gene.

Key findings: As a population, those affected with GWI exhibited an uninduced mutation frequency at the GPA locus that was effectively twice that observed in controls, a result that was statistically significant. This result was influenced by an increase in the incidence of individuals with aberrantly high mutation frequencies, seemingly higher than would be expected by dose extrapolation and consistent with the induction of localized genomic instability in the hematopoietic bone marrow stem cells. When these "outliers" were removed from consideration, the remaining affected population retained a significantly higher mean allele loss mutation frequency, suggesting that both dose-dependent bone marrow genotoxicity and induction of genomic instability are contributing to the elevation in mutation frequency in these affected veterans.

Significance: This study provides evidence that manifestation of GWI is associated with increased cumulative exposure to agents capable of inducing persistent mutations in bone marrow stem cells. Whether these mutations are involved in the clinical aspects of the condition or are simply biomarkers of overall exposure has yet to be determined. The increased incidence of genomic instability suggests that this persistent mutation can have important delayed effects on cellular integrity.

Hemorheological responses to an acute bout of maximal exercise in Veterans with Gulf War Illness

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Abstract

Background: Altered red blood cell (RBC) deformability has been reported in Veterans with Gulf War Illness (GWI) who endorse exercise-induced symptom exacerbation and fatigue. However, it is unknown whether altered RBC deformability is worsened secondary to exercise.

Objective: To evaluate RBC deformability in response to maximal exercise in individuals with and without GWI.

Methods: Seventeen Veterans with GWI and 11 controls performed maximal exercise and provided blood samples (pre-, immediately post- and 60-min post-exercise). We calculated RBC deformation at infinite stress (EI_{MAX}), shear stress for half-deformation ($SS_{1/2}$) and their ratio ($SS_{1/2}/EI_{MAX}$) via repeated measures ANOVA with group and time as factors.

Results: A moderate interaction effect ($p = 0.08$, $\eta^2_p = 0.10$), large main effect for group ($p = 0.02$, $\eta^2_p = 0.19$) and moderate main effect for time ($p = 0.20$, $\eta^2_p = 0.06$) were observed for EI_{MAX}, but only the main effect for group reached statistical significance. Changes in $SS_{1/2}$ and $SS_{1/2}/EI_{MAX}$ over time were similar between cases and controls as were main effects.

Conclusions: Veterans with GWI had more deformable RBCs in comparison to controls that was unaffected by maximal exercise. Future studies to confirm our findings and identify associated mechanisms are warranted.

Brainstem damage is associated with poorer sleep quality and increased pain in gulf war illness veterans

Life Sci. 2021 Sep 1; 280: 119724. doi: 10.1016/j.lfs.2021.119724. Epub 2021 Jun 16.

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Abstract

Aims: Gulf War Illness (GWI) is manifested as multiple chronic symptoms, including chronic pain, chronic fatigue, sleep problems, neuropsychiatric disorders, respiratory, gastrointestinal, and skin problems. No single target tissue or unifying pathogenic process has been identified that accounts for this variety of symptoms. The brainstem has been suspected to contribute to this multiple symptomatology. The aim of this study was to assess the role of the brainstem in chronic sleep problems and pain in GWI veterans.

Materials and methods: We enrolled 90 veterans (Age = 50 ± 5, 87% Male) who were deployed to the 1990-91 Gulf War and presented with GWI symptoms. Sleep quality was evaluated using the global Pittsburgh Sleep Quality Index. Pain intensities were obtained with the Brief Pain Inventory sum score. Volumes in cortical, subcortical, brainstem, and brainstem subregions and diffusion tensor metrics in 10 bilateral brainstem tracts were tested for correlations with symptom measures.

Key findings: Poorer sleep quality was significantly correlated with atrophy of the whole brainstem and brainstem subregions (including midbrain, pons, medulla). Poorer sleep quality also significantly correlated with lower fractional anisotropy in the nigrostriatal tract, medial forebrain tract, and the dorsal longitudinal fasciculus. There was a significant correlation between increased pain intensity and decreased fractional anisotropy in the dorsal longitudinal fasciculus. These correlations were not altered after controlling for age, sex, total intracranial volumes, or additional factors, e.g., depression and neurological conditions.

Significance: These findings suggest that the brainstem plays an important role in the aberrant neuromodulation of sleep and pain symptoms in GWI.

The effect of stress on the transcriptomes of circulating immune cells in patients with Gulf War Illness

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Abstract

Aims: In an effort to gain further insight into the underlying mechanisms tied to disease onset and progression of Gulf War Illness (GWI), our team evaluated GWI patient response to stress utilizing RNA-Seq.

Main methods: The protocol included blood collection before exercise challenge (baseline), at maximal exertion, and after exercise challenge (recovery - four hours post-exercise challenge). Peripheral blood mononuclear cell (PBMC) transcriptomics data were analyzed to understand why GWI patients process stressors differently from their healthy counterparts.

Key findings: Our findings validate previously identified dysregulation of immune and inflammatory pathways among GWI patients as well as highlight novel immune and inflammatory markers of disease activity. These results provide a foundation for future research efforts in understanding GWI pathophysiology and creating targeted treatments.

Significance: Gulf War Illness is a complex, chronic, and debilitating multi-system illness impacting 25%-30% of the U.S. troops deployed to the 1990-1991 Gulf War. The condition is characterized by medically unexplained fatigue and affects multiple organ systems. Because the underlying mechanisms are largely unknown, patients receive symptom-based treatment, rather than targeting fundamental biological processes. To the best of our knowledge, this is the first study that applies RNA-Seq to analyze the effect of GWI, and the response to stressors in GWI, on the transcriptomic changes in circulating immune cells.

Host gut microbiome and potential therapeutics in Gulf War Illness: A short review

Life Sci. 2021 Sep 1; 280: 119717. doi: 10.1016/j.lfs.2021.119717. Epub 2021 Jun 15.

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Abstract

Aims: Since our troops had returned from the first Persian Gulf War in 1990-91, the veterans have reported chronic multisymptomatic illness widely referred to as Gulf War Illness (GWI). We aim to review the current directions of GWI pathology research in the context of chronic multisymptomatic illness and its possible gut microbiome targeted therapies. The veterans of Gulf War show symptoms of chronic fatigue, cognitive deficits, and a subsection report of gastrointestinal complications.

Method: Efforts of finding a suitable treatment regimen and clinical management remain a challenge. More recently, we have shown that the pathology is connected to alterations in the gut microbiome, and efforts of finding a suitable regimen for gut-directed therapeutics are underway. We discuss the various clinical interventions and summarize the possible effectiveness of gut-directed therapies such as the use of short-chain fatty acids (SCFA), phenolic compounds, and their metabolites, use of probiotics, and fecal microbiota transfer.

Significance: The short review will be helpful to GWI researchers to expand their studies to the gut and find an effective treatment strategy for chronic multisymptomatic illness.

Predicting post-exertional malaise in Gulf War Illness based on acute exercise responses

Life Sci. 2021 Sep 1; 280:119701. doi: 10.1016/j.lfs.2021.119701. Epub 2021 Jun 10.

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Abstract

Aims: Post-exertional malaise (PEM) is poorly understood in Gulf War Illness (GWI). Exercise challenges have emerged as stimuli to study PEM; however, little attention has been paid to unique cardiorespiratory and perceptual responses during exercise. This study tested whether select exercise parameters explained variability in PEM responses.

Main methods: Visual analog scale (0-100) versions of the Kansas questionnaire were used for daily symptom measurements one week before and one week after 30-min of cycling at 70% heart rate reserve in 43 Veterans with GWI and 31 Veteran controls (CON). Cardiopulmonary exercise testing (CPET) methods were used to measure oxygen (VO_2), carbon dioxide (VCO_2), ventilation (VE), heart rate, work rate, and leg muscle pain. Symptom changes and CPET parameters were compared between groups with independent samples t-tests. Linear regression (GLM) with VE/VCO_2, cumulative work, leg muscle pain, and self-reported physical function treated as independent variables and peak symptom response as the dependent variable tested whether exercise responses predicted PEM.

Key findings: Compared to CON, Veterans with GWI had greater ventilatory equivalent for oxygen (VE/VO_2), peak leg muscle pain, fatigue, and lower VCO_2, VO_2, power, and cumulative work during exercise ($p < 0.05$), and greater peak symptom responses (GWI = 38.90 ± 29.06, CON = 17.84 ± 28.26, $g = 0.70$, $p < 0.01$). The final GLM did not explain significant variance in PEM (Pooled $R^2 = 0.15$, Adjusted $R^2 = 0.03$, $p = 0.34$).

Significance: The PEM response was not related to the selected combination of cardiorespiratory and perceptual responses to exercise.

Gulf War veterans exhibit broadband sleep EEG power reductions in regions overlying the frontal lobe

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Abstract

Aims: Nearly a third of U.S. veterans who deployed in support of the 1990-1991 Persian Gulf War are affected by Gulf War illness (GWI). Here we aimed to characterize whether subjective sleep complaints in GWI veterans are associated with objective sleep EEG disturbances relative to healthy veterans and controls; and whether Gulf War veterans show alterations in neural activity during sleep that differentiate them from healthy subjects.

Main methods: We used high-density EEG (HDEEG) to assess regional patterns of rapid eye movement (REM) sleep and non-REM (NREM) sleep between three groups: Gulf War male veterans with fatigue and GWI, Gulf War male veterans without fatigue or GWI, and control males. The groups were matched relative to age, sex and obstructive sleep apnea. Topographic comparisons of nocturnal NREM and REM sleep were made between groups for all frequency bands.

Key findings: Topographic analysis revealed a broadband reduction in EEG power in a circumscribed region overlying the frontal lobe in both groups of Gulf War veterans, regardless of GWI and fatigue. This frontal reduction in neural activity was present, to some extent, across all frequency bands in NREM and REM sleep.

Significance: Given that our findings were observed in all Gulf War veterans, it appears unlikely that frontal sleep HDEEG power reductions prove wholly responsible for fatigue symptoms. These results provide avenues for research which may someday contribute to improved clinical care of formerly deployed veterans of the Persian Gulf War.

The relationship between Gulf War Illness symptom severity and heart rate variability: A pilot study

Life Sci. 2021 Sep 1; 280:119663. doi: 10.1016/j.lfs.2021.119663. Epub 2021 Jun 2.

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Abstract

Introduction: Gulf War Illness (GWI) is a chronic multisymptom illness affecting 250,000+ veterans of the '90-'91 Gulf War which remains under-explored in terms of its physiological characteristics. We investigated whether subjective GWI symptom severity scores were related to objective measures of autonomic nervous system activity.

Methods: We estimated activity in the two major branches of the autonomic nervous system (the parasympathetic nervous system [PNS] and the sympathetic nervous system [SNS]) via metrics of heart rate variability in a sample of Veterans who met established criteria for GWI with varying degrees of self-reported symptom severity. We hypothesized that subjective symptom severity scores would be inversely related to PNS activity and positively related to SNS activity.

Results: Significant negative relationships were observed between the root mean square of successive differences of beat-to-beat intervals (a measure of PNS activity) and symptom severity, both overall and across specific GWI symptom categories (sp. fatigue [r = -0.574], gastrointestinal [r = -0.544]). Furthermore, significant positive relationships were observed between the cardiac sympathetic index and symptom severity, both overall and across specific symptom categories (sp. cognitive [r = 0.721], fatigue [r = 0.560], gastrointestinal [r = 0.694], skin [r = 0.686]).

Conclusions: Metrics of PNS activation revealed a negative relationship with self-reported symptom severity, while metrics of SNS activation revealed a positive relationship. The present results improve our understanding of the physiology of GWI and provide a new window from which to consider this medically unexplained illness.

Effect of the low glutamate diet on inflammatory cytokines in veterans with Gulf War Illness (GWI): A pilot study

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Abstract

Aim: To examine the effects of the low glutamate diet on inflammatory cytokines in veterans with Gulf War Illness (GWI).

Main methods: Forty veterans with GWI were recruited from across the country. Anthropometric measurements and blood samples were collected at baseline and after one month on the low glutamate diet. Dietary adherence was measured with a glutamate food frequency questionnaire (FFQ). Inflammatory cytokines (IL-1β, IL-6, IFN-γ, and TNF-α) were measured in pre- and post-diet serum (N = 34). Improvement was defined as being "much" or "very much" improved on the patient global impression of change scale (PGIC), or as having ≥30% of their symptoms remit. Correlations of the FFQ and the cytokines were calculated, followed by multivariable linear regression for significant findings. Mann Whitney U tests were used to compare cytokine levels according to improvement on the diet, and then logistic regression was used to estimate the association after adjustment for potential confounders. Classification trees were also produced to determine the ability of change in the inflammatory cytokines to predict improvement on the diet.

Key findings: Dietary adherence was significantly associated with reduction in TNF-α, and PGIC improvement was significantly associated with reduced IL-1β, after adjustment for potential confounders. Classification trees demonstrated that IL-1β, TNF-α, and IL-6 can predict improvement on the diet with 76.5% accuracy.

Significance: Findings suggest that the low glutamate diet may be able to reduce systemic inflammation in veterans with GWI.

Neurotoxicant exposures and rates of Chronic Multisymptom Illness and Kansas Gulf War Illness criteria in Gulf War deployed women veterans

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Abstract

Aims: This study analyzed deployment-related exposures and risk of Persian Gulf War Illness (GWI) in women veterans from the Veterans Affairs (VA) Cooperative Studies Program 585 Gulf War Era Cohort and Biorepository (GWECB CSP#585).

Main methods: We examined the associations between GW deployment-related exposures and case definitions for GWI in deployed GW women. Multivariate regression analyses controlling for demographic outcomes were performed.

Key findings: Surveys were obtained from 202 GW deployed women veterans. Self-reported exposure to smoke from oil well fires as well as chemical and biological warfare were the only exposures significantly associated with the Center for Disease Control and Prevention (CDC) GWI criteria. Seventy-nine women were excluded from the rest of the analyses as they met Kansas GW illness exclusion criteria. Eligible women who self-reported deployment-related exposure to smoke from oil wells, pyridostigmine bromide (PB) pills, pesticide cream, pesticide treated uniforms, and insect baits were significantly more likely to meet the Kansas GWI criteria (n = 123) than those unexposed and exposures were related to Kansas symptom subdomain endorsements.

Significance: These results suggest that women GW veterans reporting deployment related exposures of pesticide, oil well fire and PB pills are significantly more likely to meet the Kansas GWI criteria in this national cohort of GW women suggesting its utility in future studies. In addition, based on these results it appears that women exposed to particular toxicants during the war may benefit from more targeted treatment strategies dependent upon the mechanism of exposure of their toxicant induced outcomes.

Emerging role of glutamate in the pathophysiology and therapeutics of Gulf War illness

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Abstract

Gulf War illness (GWI) is a chronic and multi-symptomatic disorder affecting veterans who served in the Gulf War. The commonly reported symptoms in GWI veterans include mood problems, cognitive impairment, muscle and joint pain, migraine/headache, chronic fatigue, gastrointestinal complaints, skin rashes, and respiratory problems. Neuroimaging studies have revealed significant brain structure alterations in GWI veterans, including subcortical atrophy, decreased volume of the hippocampus, reduced total grey and white matter, and increased brain white matter axial diffusivity. These brain changes may contribute to or increase the severities of the GWI-related symptoms. Epidemiological studies have revealed that neurotoxic exposures and stress may be significant contributors to the development of GWI. However, the mechanism underlying how the exposure and stress could contribute to the multi-symptomatic disorder of GWI remains unclear. We and others have demonstrated that rodent models exposed to GW-related agents and stress exhibited higher extracellular glutamate levels, as well as impaired structure and function of glutamatergic synapses. Restoration of the glutamatergic synapses ameliorated the GWI-related pathological and behavioral deficits. Moreover, recent studies showed that a low-glutamate diet reduced multiple symptoms in GWI veterans, suggesting an important role of the glutamatergic system in GWI. Currently, growing evidence has indicated that abnormal glutamate neurotransmission may contribute to the GWI symptoms. This review summarizes the potential roles of glutamate dyshomeostasis and dysfunction of the glutamatergic system in linking the initial cause to the multi-symptomatic outcomes in GWI and suggests the glutamatergic system as a therapeutic target for GWI.

Lacto-N-fucopentaose-III (LNFPIII) ameliorates acute aberrations in hippocampal synaptic transmission in a Gulf War Illness animal model

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Abstract

Approximately one-third of Persian Gulf War veterans are afflicted by Gulf War Illness (GWI), a chronic multisymptom condition that fundamentally presents with cognitive deficits (i.e., learning and memory impairments) and neuroimmune dysfunction (i.e., inflammation). Factors associated with GWI include overexposures to neurotoxic pesticides and nerve agent prophylactics such as permethrin (PM) and pyridostigmine bromide (PB), respectively. GWI-related neurological impairments associated with PB-PM overexposures have been recapitulated in animal models; however, there is a paucity of studies assessing PB-PM-related aberrations in hippocampal synaptic plasticity and transmission that may underlie behavioral impairments. Importantly, FDA-approved neuroactive treatments are currently unavailable for GWI. In the present study, we assessed the efficacy of an immunomodulatory therapeutic, lacto-N-fucopentaose-III (LNFPIII), on ameliorating acute effects of in vivo PB-PM exposure on synaptic plasticity and transmission as well as trophic factor/cytokine expression along the hippocampal dorsoventral axis. PB-PM exposure resulted in hippocampal synaptic transmission deficits 48 h post-exposure, a response that was ameliorated by LNFPIII coadministration, particularly in the dorsal hippocampus (dH). LNFPIII coadministration also enhanced synaptic transmission in the dH and the ventral hippocampus (vH). Notably, LNFPIII coadministration elevated long-term potentiation in the dH. Further, PB-PM exposure and LNFPIII coadministration uniquely altered key inflammatory cytokine and trophic factor production in the dH and the vH. Collectively, these findings demonstrate that PB-PM exposure impaired hippocampal synaptic responses 48 h post-exposure, impairments that differentially manifested along the dorsoventral axis. Importantly, LNFPIII ameliorated GWI-related electrophysiological deficits, a beneficial effect indicating the potential efficacy of LNFPIII for treating GWI.

Gastrointestinal problems, mechanisms and possible therapeutic directions in Gulf war illness: a mini review

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Abstract

By its nature, Gulf war illness (GWI) is multisymptomatic and affects several organ systems in the body. Along with other symptoms, veterans who suffer from GWI commonly report chronic gastrointestinal issues such as constipation, pain, indigestion, etc. However, until recently, most attention has been focused on neurological disturbances such as cognitive impairments, chronic fatigue, and chronic pain among affected veterans. With such high prevalence of gastrointestinal problems among Gulf war (GW) veterans, it is surprising that there is little research to investigate the mechanisms behind these issues. This review summarizes all the available works on the mechanisms behind gastrointestinal problems in GWI that have been published to date in various databases. Generally, these studies, which were done in rodent models, in vitro and human cohorts propose that an altered microbiome, a reactive enteric nervous system or a leaky gut among other possible mechanisms are the major drivers of gastrointestinal problems reported in GWI. This review aims to draw attention to the gastrointestinal tract as an important player in GWI disease pathology and a potential therapeutic target.

Cerebrospinal Fluid MicroRNA Changes in Cognitively Normal Veterans With a History of Deployment-Associated Mild Traumatic Brain Injury

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Abstract

A history of traumatic brain injury (TBI) increases the odds of developing Alzheimer's disease (AD). The long latent period between injury and dementia makes it difficult to study molecular changes initiated by TBI that may increase the risk of developing AD. MicroRNA (miRNA) levels are altered in TBI at acute times post-injury (<4 weeks), and in AD. We hypothesized that miRNA levels in cerebrospinal fluid (CSF) following TBI in veterans may be indicative of increased risk for developing AD. Our population of interest is cognitively normal veterans with a history of one or more mild TBI (mTBI) at a chronic time following TBI. We measured miRNA levels in CSF from three groups of participants: (1) community controls with no lifetime history of TBI (ComC); (2) deployed Iraq/Afghanistan veterans with no lifetime history of TBI (DepC), and (3) deployed Iraq/Afghanistan veterans with a history of repetitive blast mTBI (DepTBI). CSF samples were collected at the baseline visit in a longitudinal, multimodal assessment of Gulf War veterans, and represent a heterogenous group of male veterans and community controls. The average time since the last blast mTBI experienced was 4.7 ± 2.2 years [1.5 – 11.5]. Statistical analysis of TaqMan™ miRNA array data revealed 18 miRNAs with significant differential expression in the group comparisons: 10 between DepTBI and ComC, 7 between DepC and ComC, and 8 between DepTBI and DepC. We also identified 8 miRNAs with significant differential detection in the group comparisons: 5 in DepTBI vs. ComC, 3 in DepC vs. ComC, and 2 in DepTBI vs. DepC. When we applied our previously developed multivariable dependence analysis, we found 13 miRNAs (6 of which are altered in levels or detection) that show dependencies with participant phenotypes, e.g., ApoE. Target prediction and pathway analysis with miRNAs differentially expressed in DepTBI vs. either DepC or ComC identified canonical pathways highly relevant to TBI including senescence and ephrin receptor signaling, respectively. This study shows that both TBI and deployment result in persistent changes in CSF miRNA levels that are relevant to known miRNA-mediated AD pathology, and which may reflect early events in AD.

Protocol for a type 1 hybrid effectiveness/implementation clinical trial of collaborative specialty care for Veterans with Gulf War Illness

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Abstract

Aims: We describe a clinical trial to determine the effectiveness and understand implementation outcomes for tele-collaborative specialty care for Veterans with GWI.

Main methods: This study will be a hybrid type 1 randomized effectiveness/implementation trial comparing tele-collaborative specialty care to electronic consultation for Gulf War Veterans with GWI (N = 220). In tele-collaborative specialty care, the specialty provider team will deliver health coaching and problem-solving treatment to Veterans and recommend a plan for analgesic optimization. In electronic consultation, the specialty provider team will make a one-time recommendation to the primary care team for locally delivered health coaching, problem-solving treatment and analgesic optimization. The primary aim will be to determine the effectiveness of tele-collaborative specialty care to reduce disability related to GWI. Our secondary aim will be to understand implementation outcomes.

Significance: There is a need to improve care for Veterans with GWI. A potentially useful model to address these barriers and improve care is tele-collaborative specialty care where the specialists work with primary care provider to synergistically treat the patients.

Discussion: This is the first clinical trial to prospectively compare different models of care for Veterans with GWI. This responds to multiple calls for research to improve treatment for Veterans with GWI, including from the National Academy of Medicine.

A cellular approach to understanding and treating Gulf War Illness

Cell Mol Life Sci. 2021 Sep 27. doi: 10.1007/s00018-021-03942-3. Online ahead of print.

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Abstract

Gulf War Illness (GWI), a disorder suffered by approximately 200,000 veterans of the first Gulf War, was caused by exposure to low-level organophosphate pesticides and nerve agents in combination with battlefield stress. To elucidate the mechanistic basis of the brain-related symptoms of GWI, human-induced pluripotent stem cells (hiPSCs) derived from veterans with or without GWI were differentiated into forebrain glutamatergic neurons and then exposed to a Gulf War (GW) relevant toxicant regimen consisting of a sarin analog and cortisol, a human stress hormone. Elevated levels of total and phosphorylated tau, reduced microtubule acetylation, altered mitochondrial dynamics/transport, and decreased neuronal activity were observed in neurons exposed to the toxicant regimen. Some of the data are consistent with the possibility that some veterans may have been predisposed to acquire GWI. Wistar rats exposed to a similar toxicant regimen showed a mild learning and memory deficit, as well as cell loss and tau pathology selectively in the CA3 region of the hippocampus. These cellular responses offer a mechanistic explanation for the memory loss suffered by veterans with GWI and provide a cell-based model for screening drugs and developing personalized therapies for these veterans.

Long-term changes in neuroimaging markers, cognitive function and psychiatric symptoms in an experimental model of Gulf War Illness

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Abstract

Aims: Gulf War Illness (GWI) is a multi-symptom disease with debilitating cognitive and emotional impairments in veterans. GWI, like epilepsy, is caused by chemical neurotoxicity and manifests from disturbances in neuronal excitability. However, the mechanisms underlying such devastating neurological and psychiatric symptoms remain unclear. Here we investigated the long-term changes in neural behavior and brain structural abnormalities in a rat model of GWI. GWI is linked to exposure to GWI-related organophosphate chemicals (pyridostigmine bromide or PB and insecticide DEET, permethrin) during the stressful Gulf war.

Methods: To mimic GWI, we generated an experimental GWI prototype in rats by daily exposure to GWI-related chemicals with restraint stress (GWIR-CS) for 4 weeks. Changes in MRI scan and cognitive function were assessed at 5- and 10- months post-exposure.

Key findings: In MRI scans, rats displayed significant increases in lateral ventricle T2 relaxation times at both 5- and 10-months after GWIR-CS, indicating alterations in the cerebrospinal fluid (CSF) density. Furthermore, at 10 months, there were significant decreases in the volumes of the hippocampus and thalamus and an increase in the lateral ventricle volume. At both time points, they exhibited impairments in multiple neurobehavioral tests, confirming substantial deficits in memory and mood function. GWI-CS rats also displayed aggressive behavior and a marked decrease in social interaction and forced swimming, indicating depression.

Conclusions: These results confirm that chronic GWIR-CS exposure led to cognitive and psychiatric symptoms with concurrent neuroimaging abnormalities in CSF, with morphological neural lesions, demonstrating the role of divergent etiological mechanisms in GWI and its comorbidities.

Pyridostigmine bromide, chlorpyrifos, and DEET combined Gulf War exposure insult depresses mitochondrial function in neuroblastoma cells

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Abstract

Gulf War Illness (GWI) is defined by the Centers for Disease Control and Prevention (CDC) as a multi-symptom illness having at least one symptom from two of three factors, which include: fatigue, mood-cognition problems, and musculoskeletal disorders. The cluster of long-term symptoms is unique to military personnel from coalition countries including United States, Australia, and the United Kingdom that served in Operation Desert Storm from 1990 to 1991. Reporting of these symptoms is much lower among soldiers deployed in other parts of the world like Bosnia during the same time period. The exact cause of GWI is unknown, but combined exposure to N,N-diethyl-m-toluamide (DEET), organophosphates like chlorpyrifos (CPF), and pyridostigmine bromide (PB), has been hypothesized as a potential mechanism. Mitochondrial dysfunction is known to occur in most neurodegenerative diseases that share symptoms with GWI and has therefore been implicated in GWI. Although exposure to these and other toxicants continues to be investigated as potential causes of GWI, their combined impact on mitochondrial physiology remains unknown. In this study, the effects of combined GWI toxicant exposure on mitochondrial function were determined in a commonly used and readily available immortalized cell line (N2a), whose higher rate of oxygen consumption resembles that of highly metabolic neurons in vivo. We report that combined exposure containing pesticide CPF 71 μM, insect repellants DEET 78 μM, and antitoxins PB 19 μM, causes profound mitochondrial dysfunction after a 4-h incubation resulting in decreased mitochondrial respiratory states in the absence of proapoptotic signaling, proton leak, or significant increase in reactive oxygen species production.