GULF WAR ILLNESS

Fatigue in Gulf War Illness is associated with tonically high activation in the executive control network.

Wylie GR[1], Genova H[2], Dobryakova E[2], DeLuca J[3], Chiaravalloti N[2], Falvo M[4], Cook D[5].

Neuroimage Clin. **2018 Dec 11**:101641. doi: 10.1016/j.nicl.2018.101641. PMID: 30558870. [Epub ahead of print]

Gulf War Illness (GWI) is a chronic, multi-symptom illness that affects approximately 25% of Gulf veterans, with cognitive fatigue as one of its primary symptoms. Here, we investigated the neural networks associated with cognitive fatigue in GWI by asking 35 veterans with GWI and 25 healthy control subjects to perform a series of fatiguing tasks while in the MRI scanner. Two types of cognitive fatigue were assessed: state fatigue, which is the fatigue that developed as the tasks were completed, and trait fatigue, or one's propensity to experience fatigue when assessed over several weeks. Our results showed that the neural networks associated with state and trait fatigue differed. Irrespective of group, the network underlying trait fatigue included areas associated with memory whereas the neural network associated with state fatigue included key areas of a fronto-striatal-thalamic circuit that has been implicated in fatigue in other populations. As in other investigations of fatigue, the caudate of the basal ganglia was implicated in fatigue. Furthermore, individuals with GWI showed greater activation than the HC group in frontal and parietal areas for the less difficult task. This suggests that an inability to modulate brain activation as task demands change may underlie fatigue in GWI.

CHRONIC FATIGUE SYNDROME

Red blood cell deformability is diminished in patients with Chronic Fatigue Syndrome.

Saha KA[1,2], Schmidt RB[1], Wilhelmy J[2], Nguyen V[1], Abugherir A[1], Do KJ[1], Nemat-Gorgani M[2], Davis WR[2], Ramasubramanian KA[1].

Clin Hemorheol Microcirc. **2018 Dec 28**. doi: 10.3233/CH-180469. PMID: 30594919. [Epub ahead of print]

BACKGROUND: Myalgic encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a poorly understood disease. Amongst others symptoms, the disease is associated with profound fatigue, cognitive dysfunction, sleep abnormalities, and other symptoms that are made worse by physical or mental exertion. While the etiology of the disease is still debated, evidence suggests oxidative damage to immune and hematological systems as one of the pathophysiological mechanisms of the disease. Since red blood cells (RBCs) are well-known scavengers of oxidative stress, and are critical in microvascular perfusion and tissue oxygenation, we hypothesized that RBC deformability is adversely affected in ME/CFS.

METHODS: We used a custom microfluidic platform and high-speed microscopy to assess the difference in deformability of RBCs obtained from ME/CFS patients and age-matched healthy controls.

RESULTS AND CONCLUSION: We observed from various measures of deformability that the RBCs isolated from ME/CFS patients were significantly stiffer than those from healthy controls. Our observations suggest that RBC transport through microcapillaries may explain, at least in part, the ME/CFS phenotype, and promises to be a novel first-pass diagnostic test.

HEADACHE and MIGRAINE

The IASP classification of chronic pain for ICD-11: chronic secondary headache or orofacial pain.

Benoliel R[1], Svensson P[2], Evers S[3], Wang SJ[4,5], Barke A[6], Korwisi B[6], Rief W[6], Treede RD[7]; IASP Taskforce for the Classification of Chronic Pain.

Pain. **2019 Jan**;160(1):60-68. doi: 10.1097/j.pain.0000000000001435. PMID: 30586072.

This article describes chronic secondary headache and chronic orofacial pain (OFP) disorders with respect to the new International Classification of Diseases (ICD-11). The section refers extensively to the International Classification of Headache Disorders (ICHD-3) of the International Headache Society that is implemented in the chapter on Neurology in ICD-11. The ICHD-3 differentiates between primary (idiopathic) headache disorders, secondary (symptomatic) headache disorders, and OFP disorders including cranial neuralgias. Chronic headache or OFP is defined as headache or OFP that occurs on at least 50% of the days during at least 3 months and lasting at least 2 hours per day. Only chronic secondary headache and chronic secondary OFP disorders are included here; chronic primary headache or OFP disorders are listed under chronic primary pain syndromes that have been described in a companion publication. The subdivisions of chronic secondary OFP of ICHD-3 are complemented by the Diagnostic Criteria for Temporomandibular Disorders and contributions from the International Association for the Study of Pain Special Interest Group on Orofacial and Head Pain and include chronic dental pain. The ICD-11 codes described here are intended to be used in combination with codes for the underlying diseases, to identify patients who require specialized pain management. In addition, these codes shall enhance visibility of these disorders in morbidity statistics and motivate research into their mechanisms.

Age-specific and gender-dependent impact of primary headache disorders on dementia risk: Population-based longitudinal study.

Yin JH[1,2], Tsai CL[1], Lee PJ[3], Chou CH[1, 4], Chen SY[5,6,7], Chung CH[8,9,10], Chien WC[9,10], Lin CC[1], Sung YF[1], Yang FC[1], Tsai CK[1], Lee JT[1,4].

Medicine (Baltimore). **2018 Dec**;97(52):e13789. doi: 10.1097/MD.0000000000013789. PMID: 30593163.

Dementia is a global burden of public health. Headache disorders are the third most common cause of disability worldwide and common problems in the elderly population. Few studies focused on the relationship between primary headache disorders (PHDs) and cognitive status, and the results remain controversial. The aim of this countrywide, population-based, retrospective study was to investigate potential association between PHDs and dementia risk. We enrolled 1346 cases with PHDs to match the 5384 individuals by age, gender and co-morbidities. The definition of PHDs, dementia, and risk factors of dementia was identified according to The International Classification of Diseases, Ninth Revision, Clinical Modification. Cox regression was administered for estimating hazard ratios (HR) for dementia. During more than 5 years of follow-up, PHDs individuals had 1.52 times ($P<.05$) greater risk to develop all dementia compared with individuals without PHDs. Elderly (aged ≥65 years) patients with PHDs displayed significantly higher risk to develop all dementia ($P<.01$) and non-Alzheimer non-vascular dementia (NAVD) $P<.01$). Female PHDs individuals were at higher risk of suffering from all dementia ($P<.05$) and NAVD ($P<.05$). The influence of PHDs on all dementia was highest in the first 2 years of observation. The results indicated PHDs are linked to a temporarily increased risk for dementia, mainly NAVD, with age-specific and gender-dependent characteristics.

HEADACHE and MIGRAINE (Continued)

Preventive effects of galcanezumab in adult patients with episodic or chronic migraine are persistent: data from the phase 3, randomized, double-blind, placebo-controlled EVOLVE-1, EVOLVE-2, and REGAIN studies.

Förderreuther S[1], Zhang Q[2], Stauffer VL[3], Aurora SK[4], Láinez MJA[5].

J Headache Pain. **2018 Dec 29**;19(1):121. doi: 10.1186/s10194-018-0951-2. PMID: 30594122.

BACKGROUND: Maintenance of effect following treatment with galcanezumab compared to placebo in adult patients with episodic or chronic migraine was evaluated.

METHODS: In 2 similarly designed studies of patients with episodic migraine (6 months) and 1 study of patients with chronic migraine (3 months), patients randomized in a 1:1:2 ratio received a subcutaneous injection of galcanezumab 120 mg/month (after an initial loading dose of 240 mg) or 240 mg/month or placebo. Maintenance of effect during the double-blind phase was evaluated based on a comparison of the percentages of galcanezumab- and placebo-treated patients with maintenance of 30, 50, 75, and 100% response (defined as ≥30, ≥50, ≥75, and 100% reduction from baseline in monthly migraine headache days [MHD]) at an individual patient level. Logistic regression analyses were used for between treatment comparisons.

RESULTS: A total of 1773 adult patients with episodic migraine (n = 444 for galcanezumab 120 mg; n = 435 for galcanezumab 240 mg; n = 894 for placebo for 2 studies pooled) and 1113 patients with chronic migraine (n = 278 for galcanezumab 120 mg; n = 277 for galcanezumab 240 mg; n = 558 for placebo) were evaluated. In patients with episodic migraine, ≥50% response was maintained in 41.5 and 41.1% of galcanezumab-treated patients (120 mg and 240 mg, respectively) for ≥3 consecutive months (until patient's endpoint) and 19.0 and 20.5%, respectively, for 6 consecutive months and was significantly greater than the 21.4 and 8.0% of placebo-treated patients at ≥3 and 6 months consecutively (P < 0.001). Approximately 6% of galcanezumab-treated patients maintained ≥75% response all 6 months versus 2% of placebo-treated patients. Few galcanezumab-treated patients maintained 100% response. In patients with chronic migraine, 29% of galcanezumab-treated patients maintained ≥30% response all 3 months compared to 16% of placebo patients while ≥50% response was maintained in 16.8 and 14.6% of galcanezumab-treated patients (120 mg and 240 mg) and was greater than placebo (6.3%; p < 0.001). Few patients maintained ≥75% response.

CONCLUSIONS: Treatment with galcanezumab 120 mg or 240 mg demonstrated statistically significant and clinically meaningful persistence of effect in patients with episodic migraine (≥3 and 6 consecutive months) and in patients with chronic migraine (for 3 months).

STUDY IDENTIFICATION AND TRIAL REGISTRATION: Study Identification: EVOLVE-1 (I5Q-MC-CGAG); EVOLVE-2 (I5Q-MC-CGAH); REGAIN (I5Q-MC-CGAI). Trial Registration: ClinicalTrials.gov; **NCT02614183** (EVOLVE-1); **NCT02614196** (EVOLVE-2); **NCT02614261** (REGAIN).

Botulinum Toxin versus Placebo: A Meta-Analysis of Prophylactic Treatment for Migraine.

Bruloy E[1], Sinna R, Grolleau JL, Bout-Roumazeilles A, Berard E, Chaput B.

Plast Reconstr Surg. **2019 Jan**;143(1):239-250. doi: 10.1097/PRS.0000000000005111. PMID: 30589800.

BACKGROUND: The purpose of this study was to assess the efficacy of botulinum toxin in reducing the frequency of migraine headaches.

METHODS: The MEDLINE, Embase, and Cochrane Library databases were searched to identify randomized, double-blind, placebo-controlled trials that compared patients receiving botulinum toxin versus placebo injections in the head and neck muscles, for the preventive treatment of migraine. The primary outcome was change in the number of headache episodes per month from baseline to 3 months.

RESULTS: There were 17 studies including a total of 3646 patients. Overall analysis reported a tendency in favor of botulinum toxin over placebo at 3 months, with a mean difference in the change of migraine frequency of -0.23 (95 percent CI, -0.47 to 0.02; p = 0.08). The reduction in frequency of chronic migraines was significant, with a mean differential change of -1.56 (95 percent CI, -3.05 to -0.07; p = 0.04). Analysis of chronic migraine frequency was also significant after 2 months. The findings also highlighted an improvement of the patient's quality of life at 3 months in the botulinum toxin group (p < 0.00001). Further adverse events were traced in the botulinum toxin type A group with a statistically significant risk ratio of 1.32 (p = 0.002).

CONCLUSIONS: This meta-analysis reveals that botulinum toxin type A injections are superior to placebo for chronic migraines after 3 months of therapy. For the first time, a real benefit in patient quality of life is demonstrated with only few and mild adverse events.

CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, II.

CHRONIC PAIN

Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis.

Busse JW[1,2,3,4], Wang L[1,2,5], Kamaleldin M[6], Craigie S[3], Riva JJ[3,7], Montoya L[8], Mulla SM[3,9], Lopes LC[10], Vogel N[11], Chen E[12], Kirmayr K[13], De Oliveira K[14], Olivieri L[15], Kaushal A[1,3,16], Chaparro LE[17], Oyberman I[17], Agarwal A[3,18], Couban R[1], Tsoi L[19], Lam T[20], Vandvik PO[21], Hsu S[3], Bala MM[22], Schandelmaier S[3,23,24], Scheidecker A[2,25], Ebrahim S[3], Ashoorion V[1,26], Rehman Y[1,27], Hong PJ[28], Ross S[3], Johnston BC[3,29], Kunz R[24], Sun X[3,5], Buckley N[1,2], Sessler DI[30], Guyatt GH[3].

JAMA. **2018 Dec 18**;320(23):2448-2460. doi: 10.1001/jama.2018.18472. PMID: 30561481.

Importance: Harms and benefits of opioids for chronic noncancer pain remain unclear.

Objective: To systematically review randomized clinical trials (RCTs) of opioids for chronic noncancer pain.

Data Sources and Study Selection: The databases of CENTRAL, CINAHL, EMBASE, MEDLINE, AMED, and PsycINFO were searched from inception to April 2018 for RCTs of opioids for chronic noncancer pain vs any nonopioid control.

Data Extraction and Synthesis: Paired reviewers independently extracted data. The analyses used random-effects models and the Grading of Recommendations Assessment, Development and Evaluation to rate the quality of the evidence.

Main Outcomes and Measures: The primary outcomes were pain intensity (score range, 0-10 cm on a visual analog scale for pain; lower is better and the minimally important difference [MID] is 1 cm), physical functioning (score range, 0-100 points on the 36-item Short Form physical component score [SF-36 PCS]; higher is better and the MID is 5 points), and incidence of vomiting.

Results: Ninety-six RCTs including 26 169 participants (61% female; median age, 58 years [interquartile range, 51-61 years]) were included. Of the included studies, there were 25 trials of neuropathic pain, 32 trials of nociceptive pain, 33 trials of central sensitization (pain present in the absence of tissue damage), and 6 trials of mixed types of pain. Compared with placebo, opioid use was associated with reduced pain (weighted mean difference [WMD], -0.69 cm [95% CI, -0.82 to -0.56 cm] on a 10-cm visual analog scale for pain; modeled risk difference for achieving the MID, 11.9% [95% CI, 9.7% to 14.1%]), improved physical functioning (WMD, 2.04 points [95% CI, 1.41 to 2.68 points] on the 100-point SF-36 PCS; modeled risk difference for achieving the MID, 8.5% [95% CI, 5.9% to 11.2%]), and increased vomiting (5.9% with opioids vs 2.3% with placebo for trials that excluded patients with adverse events during a run-in period). Low- to moderate-quality evidence suggested similar associations of opioids with improvements in pain and physical functioning compared with nonsteroidal anti-inflammatory drugs (pain: WMD, -0.60 cm [95% CI, -1.54 to 0.34 cm]; physical functioning: WMD, -0.90 points [95% CI, -2.69 to 0.89 points]), tricyclic antidepressants (pain: WMD, -0.13 cm [95% CI, -0.99 to 0.74 cm]; physical functioning: WMD, -5.31 points [95% CI, -13.77 to 3.14 points]), and anticonvulsants (pain: WMD, -0.90 cm [95% CI, -1.65 to -0.14 cm]; physical functioning: WMD, 0.45 points [95% CI, -5.77 to 6.66 points]).

Conclusions and Relevance: In this meta-analysis of RCTs of patients with chronic noncancer pain, evidence from high-quality studies showed that opioid use was associated with statistically significant but small improvements in pain and physical functioning, and increased risk of vomiting compared with placebo. Comparisons of opioids with nonopioid alternatives suggested that the benefit for pain and functioning may be similar, although the evidence was from studies of only low to moderate quality.

CHRONIC PAIN (Continued)

A Two-Year Prospective Multicenter Study of Opioid Therapy for Chronic Noncancer Pain: Prescription Trends and Predictors.

Veiga DR[1], Mendonça L[2], Sampaio R[3,4,5,6], Castro-Lopes JM[2,3,4,5], Azevedo LF[2,7,8].

Pain Med. **2018 Dec 26**. doi: 10.1093/pm/pny275. PMID: 30590762. [Epub ahead of print]

Objectives: Opioid use in chronic pain has increased worldwide in recent years. The aims of this study were to describe the trends and patterns of opioid therapy over two years of follow-up in a cohort of chronic noncancer pain (CNCP) patients and to assess predictors of long-term opioid use and clinical outcomes.

Methods: A prospective cohort study with two years of follow-up was undertaken in four multidisciplinary chronic pain clinics. Demographic data, pain characteristics, and opioid prescriptions were recorded at baseline, three, six, 12, and 24 months.

Results: Six hundred seventy-four CNCP patients were recruited. The prevalence of opioid prescriptions at baseline was 59.6% (N = 402), and 13% (N = 86) were strong opioid prescriptions. At 24 months, opioid prescription prevalence was as high as 74.3% (N = 501), and strong opioid prescription was 31% (N = 207). Most opioid users (71%, N = 479) maintained their prescription during the two years of follow-up. Our opioid discontinuation was very low (1%, N = 5). Opioid users reported higher severity and interference pain scores, both at baseline and after two years of follow-up. Opioid use was independently associated with continuous pain, pain location in the lower limbs, and higher pain interference scores.

Conclusions: This study describes a pattern of increasing opioid prescription in chronic pain patients. Despite the limited improvement of clinical outcomes, most patients keep their long-term opioid prescriptions. Our results underscore the need for changes in clinical practice and further research into the effectiveness and safety of chronic opioid therapy for CNPC.

Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11).

Treede RD[1], Rief W[2], Barke A[2], Aziz Q[3], Bennett MI[4], Benoliel R[5], Cohen M[6], Evers S[7], Finnerup NB[8,9], First MB[10], Giamberardino MA[11], Kaasa S[12,13,14], Korwisi B[2], Kosek E[15], Lavand'homme P[16], Nicholas M[17], Perrot S[18], Scholz J[19], Schug S[20,21], Smith BH[22], Svensson P[23,24], Vlaeyen JWS[25,26,27], Wang SJ[28,29].

Pain. **2019 Jan**;160(1):19-27. doi: 10.1097/j.pain.0000000000001384.

Chronic pain is a major source of suffering. It interferes with daily functioning and often is accompanied by distress. Yet, in the International Classification of Diseases, chronic pain diagnoses are not represented systematically. The lack of appropriate codes renders accurate epidemiological investigations difficult and impedes health policy decisions regarding chronic pain such as adequate financing of access to multimodal pain management. In cooperation with the WHO, an IASP Working Group has developed a classification system that is applicable in a wide range of contexts, including pain medicine, primary care, and low-resource environments. Chronic pain is defined as pain that persists or recurs for more than 3 months. In chronic pain syndromes, pain can be the sole or a leading complaint and requires special treatment and care. In conditions such as fibromyalgia or nonspecific low-back pain, chronic pain may be conceived as a disease in its own right; in our proposal, we call this subgroup "chronic primary pain." In 6 other subgroups, pain is secondary to an underlying disease: chronic cancer-related pain, chronic neuropathic pain, chronic secondary visceral pain, chronic posttraumatic and postsurgical pain, chronic secondary headache and orofacial pain, and chronic secondary musculoskeletal pain. These conditions are summarized as "chronic secondary pain" where pain may at least initially be conceived as a symptom. Implementation of these codes in the upcoming 11th edition of International Classification of Diseases will lead to improved classification and diagnostic coding, thereby advancing the recognition of chronic pain as a health condition in its own right.

CHRONIC PAIN (Continued)

Clustering a large Spanish sample of patients with fibromyalgia using the FIQR: differences in clinical outcomes, economic costs, inflammatory markers, and gray matter volumes.

Pérez-Aranda A[1,2,3,4], Andrés-Rodríguez L[1,2,3], Feliu-Soler A[1,2,3], Núñez C[2,5], Stephan-Otto C[2,5,6], Pastor-Mira MA[7], López-Roig S[7], Peñacoba C[8], Calandre EP[9], Slim M[10], Salgueiro M[11], Feixas G[4,12], Luciano JV[1,2,3].

Pain. **2018 Dec 21**. doi: 10.1097/j.pain.0000000000001468. PMID: 30586023. [Epub ahead of print]

The main objective of this study is to identify fibromyalgia syndrome (FMS) clusters using the Revised Fibromyalgia Impact Questionnaire (FIQR); and to examine whether the clusters differ in sociodemographic characteristics, clinical measures, direct and indirect costs, levels of inflammatory markers and brain morphometry. A hierarchical cluster analysis was performed to classify a large, pooled Spanish sample of patients with FMS (N= 947) using the FIQR as clustering variable. A latent profile analysis was subsequently conducted to confirm the optimal number of FMS clusters. To examine external validity, a battery of clinical measures, economic costs, inflammatory markers and gray matter volumes of relevant cortical and subcortical areas were analyzed. We also compared the discriminant validity of the clusters with the original FIQR severity categories. To promote the implementation in real-world clinical practice, we built a free online cluster calculator. Our findings indicated that a four-cluster solution more clearly captured the heterogeneity of FIQR data and provided the best fit. This cluster solution allowed detection of differences for most clinical outcomes and economic costs. Regarding the inflammatory and brain-based biomarkers, differences were found in C-reactive protein, and tendencies were found in the right medial prefrontal cortex, the right parahippocampal gyrus, and the right middle cingulate cortex; brain regions associated with executive functions and pain processing. The original FIQR categories presented similar results, although their precision in discriminating among the non-extreme categories (i.e., moderate and severe) was not sound. These findings are discussed in relation to previous research on FMS clustering.

OTHER RESEARCH OF INTEREST

Double-Blind Placebo-Controlled Study of Rifaximin and Lactulose Hydrogen Breath Test in Gulf War Veterans with Irritable Bowel Syndrome.

Tuteja AK[1,2], Talley NJ[3], Stoddard GJ[4], Verne GN[5,6].

Dig Dis Sci. **2018 Oct 28**. doi: 10.1007/s10620-018-5344-5. PMID: 30370492. [Epub ahead of print]

BACKGROUND: Irritable bowel syndrome (IBS) occurs in up to 33% of Gulf War (GW) Veterans. Alterations in gut microflora including small intestinal bacterial overgrowth (SIBO) during deployment may play a role in development of IBS. Rifaximin is a minimally absorbed antibiotic speculated to improve IBS symptoms, in part, by restoring normal gut microflora. The aim of this study was to compare rifaximin to placebo on IBS symptoms and quality of life (QOL) in GW Veterans with IBS without constipation.

METHODS: A double-blind, placebo-controlled study was performed. One hundred and twenty-two GW Veterans with IBS (Rome III) from our database and referral to gastroenterology and internal medicine clinics were screened. After a 2-week run-in period, 50 patients were randomized (1:1) to receive either rifaximin 550 gm or placebo twice daily for 2 weeks in a double-blind study. Patients were advised not to change their diet or medications during the study. The symptoms assessed were: (1) stool frequency, (2) stool consistency (Bristol stool scale, 1-7, very hard to watery), (3) urgency (1 = yes/0 = no daily for 7 days), (4) severity of abdominal pain (0-4, none to severe), (5) severity of bloating (1-4, none to severe), and (6) global improvement scale (1-7, substantially worse to substantially improved). These were recorded for 7 consecutive days and then averaged across the 7 days, to generate a continuous variable. The symptom data were compared after 2 weeks of treatment. QOL was assessed using IBS-QOL. The lactulose hydrogen breath test (LHBT) was performed at baseline and after 2 weeks of treatment.

RESULTS: Fifty Veterans were randomized to receive treatment; 3 withdrew and 3 were lost to follow-up. Data were analyzed from 44 patients (38 men, 6 women, median age 52, range 33-77 years). Rifaximin was not associated with significant improvement in global symptoms, abdominal pain, bloating, stool urgency, frequency, or consistency (all P ≥ 0.25) or QOL (all P ≥ 0.26). Normalization of SIBO by LHBT was not different between rifaximin- and placebo-treated Veterans (7 vs. 22%, P = 0. 54).

CONCLUSION: Rifaximin was not effective in improving IBS symptoms and QOL in GW Veterans with non-constipated IBS.

OTHER RESEARCH OF INTEREST (Continued)

Birth Defects Among 788 Children Born to Gulf War Veterans Based on Physical Examination.

Shinawi MS[1], Alpern R, Toomey R, Dannenfeldt DS, Reda D, Blanchard M.

J Occup Environ Med. **2018 Nov 26**. doi: 10.1097/JOM.0000000000001508. PMID: 30489351. [Epub ahead of print]

OBJECTIVE: The aim of the study was to examine the prevalence of birth defects among children born to Gulf War veterans.

METHODS: 788 singleton children born after the war to 522 veterans (262 Gulf War-deployed, DV; 260 non-deployed, NDV) underwent physical examinations focusing on major and minor birth defects and other findings.

RESULTS: We found no differences between children of DV and NDV in the prevalence of major birth defects or other findings. However, children of DV females were more likely to have minor birth defects compared to children of NDV females (DV 22% NDV 4.8%, OR:5.47, CI: 2.06,14.55), mainly due to increased incidence of minor eye and musculoskeletal birth defects.

CONCLUSIONS: Our data show that deployment of females to the Persian Gulf arena was associated with increased risk of minor birth defects in their offspring.

White matter microstructural abnormalities in blast-exposed combat veterans: accounting for potential pre-injury factors using consanguineous controls.

McClelland AC[1,2], Fleysher R[1,2], Mu W[1], Kim N[1,2], Lipton ML[3,4].

Neuroradiology. **2018 Oct**;60(10):1019-1033. doi: 10.1007/s00234-018-2070-9. PMID: 30116841. Epub 2018 Aug 17.

PURPOSE: Assess the prevalence of white matter microstructural changes in combat veterans, within the context of a highly matched control group comprising unexposed close relatives.

METHODS: This prospective study had institutional review board approval, included written informed consent, and is HIPAA-compliant. Diffusion tensor imaging was analyzed in 16 male blast-exposed combat veterans of Operation Iraqi Freedom/Operation Enduring Freedom (mean age 31.0 years) and 18 unexposed males (mean age 30.4 years) chosen on the basis of a consanguineous relationship to a member of the subject group. Whole-brain voxel-based comparison of fractional anisotropy (FA) was performed using both group and individual analyses. Areas where effects on FA were detected were subsequently characterized by extracting radial diffusivity (RD), axial diffusivity (AD), and mean diffusivity (MD) from the regions of abnormal FA.

RESULTS: Controls did not differ from veterans on any background demographic factor. In voxel-based group comparison, we identify high fractional anisotropy (FA) in veterans compared to controls ($p < 0.01$). Within individual veterans, we find multiple areas of both abnormally high and low FA ($p < 0.01$) in a heterogeneous distribution, consistent with multifocal traumatic axonal injury. In individualized analyses, low FA areas demonstrate high radial diffusivity, whereas high FA areas demonstrate low RD in both group and individual analyses.

CONCLUSIONS: Combat-related blast exposure is associated with microstructural white matter abnormalities, and the nature of the control group decreases the likelihood that the findings reflect underlying background differences. Abnormalities are heterogeneously distributed across patients, consistent with TAI, and include areas of low and high FA.

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