GULF WAR ILLNESS

**Association among anterior cingulate cortex volume, psychophysiological response, and PTSD diagnosis in a Veteran sample.**

Young DA1, Chao L2, Neylan TC3, O'Donovan A3, Metzler TJ3, Inslicht SS3.


Posttraumatic stress disorder (PTSD) is associated with fear response system dysregulation. Research has shown that the anterior cingulate cortex (ACC) may modulate the fear response and that individuals with PTSD have abnormalities in ACC structure and functioning. Our objective was to assess whether ACC volume moderates the relationship between PTSD and fear-potentiated psychophysiological response in a sample of Gulf War Veterans. 142 Veteran participants who were associated with a larger study associated with Gulf War Illness were exposed to no threat, ambiguous threat, and high threat conditions in a fear conditioned startle response paradigm and also provided MRI imaging data. PTSD was assessed using the Clinician Administered PTSD Scale (CAPS). Decreased caudal ACC volume predicted greater psychophysiological responses with a slower habituation of psychophysiological magnitudes across trials (p < 0.001). PTSD diagnosis interacted significantly with both caudal and rostral ACC volumes on psychophysiological response magnitudes, where participants with PTSD and smaller rostral and caudal ACC volumes had greater psychophysiological magnitudes across trials (p < 0.05 and p < 0.001, respectively) and threat conditions (p < 0.05 and p < 0.005). Our results suggest that ACC volume may moderate both threat sensitivity and threat response via impaired habituation in individuals who have been exposed to traumatic events. More research is needed to assess whether ACC size and these associated response patterns are due to neurological processes resulting from trauma exposure or if they are indicative of a premorbid risk for PTSD subsequent to trauma exposure.

CHRONIC FATIGUE SYNDROME

**The associated features of multiple somatic symptom complexes.**


OBJECTIVE: To assess whether two or more functional somatic symptom complexes (SSCs) showed stronger association with psychosocial correlates than single or no SSC after adjustment for depression/anxiety and general medical disorders.

METHODS: In a population-based sample we identified, by standardised questionnaire, participants with chronic widespread pain, chronic fatigue and irritable bowel syndrome, excluding those with a medical cause for pain/fatigue. We compared psychosocial variables in three groups: multiple (≥1), single or no FSS, adjusting for depression/anxiety and general medical disorders using ordinal logistic regression. We evaluated whether multiple SSCs predicted greater health status 1 year later using multiple regression to adjust for confounders.

RESULTS: complexes, 16.2% a single symptom complex. Many psychosocial adversities were significantly associated with number of SSCs in the expected direction but, for many, statistical significance was lost after adjustment for depression/anxiety and medical illness. Somatic symptoms, health anxiety, impairment and number of prior doctor visits remained significantly associated. Impaired health status 1 year later was predicted by multiple somatic symptom complexes even after adjustment for depression, anxiety, medical disorders and number of symptoms.

CONCLUSIONS: Depression, anxiety, medical illness and health anxiety, demonstrated an exposure-response relationship with number of somatic symptom complexes. These may be core features of all Functional Somatic Syndromes and may explain why number of somatic symptom complexes predicted subsequent health status. These features merit inclusion in prospective studies to ascertain causal relationships.
CHRONIC FATIGUE SYNDROME (Continued)


Dry eye syndrome and the subsequent risk of chronic fatigue syndrome—A prospective population-based study in Taiwan.
Chen CS1,2,3, Cheng HM4,5, Chen HJ6,7,8, Tsai SY9,10, Kao CH11,12,13, Lin HJ14,15, Wan L15,16,17,18, Yang TY19,20,21.

Background and Aim: The clinical association between dry eye syndrome (DES) and chronic fatigue syndrome (CFS) remain unclear with less evidences. We aimed to investigate the relationship between CFS and DES using a national insurance and prospective cohort study.

Methods: Data from the Longitudinal Health Insurance Database 2000 was applied to estimate the incidence of CFS among patients with DES, and their age- and sex-matched controls without DES over a long-term follow-up period. All participants were CFS free at baseline, before the interval (2005-2007), but were later diagnosed with CFS. DES patients and its relative matched controls were excluded prevalent CFS before the same interval.

Results: We identified 884 patients with DES and 3,536 matched controls in baseline and estimated the hazard ratios for incident CFS in the follow-up period. Patients with DES had a 2.08-fold considerably increasing risk of developing CFS, compared to non-DES group. An elevated risk of developing CFS remained (1.61-fold risk) even after adjusting for age, sex, and comorbidities. There was a presence of increasing risk in DES-related CFS when CFS-related comorbidities existing (adjusted hazard ratio, 1.98, 95% confidence interval, 1.19-3.29; \( p < 0.01 \)). The subsequent risk for CFS between DES and non-DES patients was significant increased with three or more annual medical visits, the adjusted risk for CFS was 4.88-fold risk (95% CI, 2.26-10.58, \( p < 0.001 \)).

Conclusion: We recommended that physicians should be aware of the increased risk of CFS among DES patients and adequately assess the health impacts among these patients.

Multidisciplinary rehabilitation treatment is not effective for myalgic encephalomyelitis/chronic fatigue syndrome: A review of the FatiGo trial.
Vink M1, Vink-Niese A2.

The FatiGo trial concluded that multidisciplinary rehabilitation treatment is more effective for chronic fatigue syndrome/myalgic encephalomyelitis in the long term than cognitive behaviour therapy and that multidisciplinary rehabilitation treatment is more cost-effective for fatigue and cognitive behaviour therapy for quality of life. However, FatiGo suffered from a number of serious methodological flaws. Moreover, it ignored the results of the activity metre, its only objective outcome. This jeopardizes the validity of FatiGo. Its analysis shows that there was no statistically significant difference between multidisciplinary rehabilitation treatment and cognitive behaviour therapy and neither are (cost-)effective. FatiGo's claims of efficacy of multidisciplinary rehabilitation treatment and cognitive behaviour therapy for chronic fatigue syndrome/myalgic encephalomyelitis are misleading and not justified by their results.
HEADACHE and MIGRAINE

Migraine-related disability, impact, and health-related quality of life among patients with episodic migraine receiving preventive treatment with erenumab.

Buse DC1, Lipton RB1, Hallström Y2, Reuter U3, Tepper SJ4, Zhang F5, Sapra S6, Picard H7, Mikol DD7, Lenz RA7.


Background: We evaluated the effect of erenumab, a fully human monoclonal antibody that inhibits the canonical calcitonin gene-related peptide receptor, on migraine-related disability, impact, and health-related quality of life among patients with episodic migraine.

Methods: Patients enrolled in a phase 3, 6-month, double-blind, placebo-controlled study of once-monthly erenumab 70 and 140 mg for migraine prevention (STRIVE) used an eDiary during the baseline and double-blind treatment phases to complete validated, specific questionnaires, including the modified (monthly) Migraine Disability Assessment Questionnaire; Headache Impact Test; and Migraine-Specific Quality of Life Questionnaire-role function-restrictive (MSQ-RFR), -role function-preventive (MSQ-RFP), and -emotional function (MSQ-EF).

Results: A total of 955 patients were randomized to receive erenumab 70 mg (n = 317), erenumab 140 mg (n = 319), or placebo (n = 319). Erenumab versus placebo resulted in significantly greater improvements in all patient-reported outcomes; changes from baseline were numerically higher with 140 mg erenumab. Improvements occurred rapidly and were maintained over 6 months of treatment. Between-group differences from placebo over months 4-6 for the 70- and 140-mg dose groups were, respectively, -2.1 and -2.8 for modified (monthly) Migraine Disability Assessment Questionnaire; Headache Impact Test; and Migraine-Specific Quality of Life Questionnaire-role function-restrictive (MSQ-RFR), -role function-preventive (MSQ-RFP), and -emotional function (MSQ-EF).

Conclusion: Erenumab reduced migraine disability and impact and improved patients' health-related quality of life, reinforcing its role as a promising new therapy for migraine prevention.

Benefits of an on-line migraine education video for patients with co-occurring migraine and depression.

Thakur E1, Recober A2, Turvey C3, Dindo LN4.


OBJECTIVE: To evaluate effects of an online, hour-long migraine education and management education program on health outcomes in people with migraine experiencing significant depressive symptoms.

METHODS: Eligible individuals in the community with comorbid migraine and depressive symptoms (n = 95) participated in the 12-week study. Participants completed self-report questionnaires examining general functioning, headache-specific disability, migraine frequency, pain, and depressive symptoms, before, and at 2, 6, and 12 weeks following the migraine education and management program. Primary analyses evaluated change over time in each outcome, using individual linear growth curve models.

RESULTS: After watching the migraine education and management video, there were significant effects of time (across all time points) for average pain level in the past 30 days (b = -0.20, p < .001), most intense pain level in the past 30 days (b = -0.33, p < .001) depression (Patient Health Questionnaire-8; b = -0.28, p = .002), and headache-specific disability (Headache Disability Inventory; b = -1.32, p < .001), such that each of these outcomes improved linearly over time.

CONCLUSIONS: A brief, online educational video is practical and effective and can lead to enhanced migraine knowledge and self-management skills and lessen the burden of migraine and concurrent depressive symptoms.
HEADACHE and MIGRAINE (Continued)

**Intracortical facilitation within the migraine motor cortex depends on the stimulation intensity.**

A paired-pulse TMS study.

Cosentino G1, Di Marco S1, Ferlisi S1, Valentino F1, Capitano WM1, Fierro B1, Brighina F2.


INTRODUCTION: Connectivity within the primary motor cortex can be measured using the paired-pulse transcranial magnetic stimulation (TMS) paradigm. This evaluates the effect of a first conditioning stimulus on the motor evoked potential (MEP) elicited by a second test stimulus when different interstimulus intervals are used. Aim of the present study was to provide, in patients suffering from migraine without aura (MwoA), additional information on intracortical facilitation (ICF), short intracortical inhibition (SICI), and long intracortical inhibition (LICI), using different intensities of the test stimulus (TS).

METHODS: We enrolled 24 patients with episodic MwoA and 24 age- and sex-matched healthy volunteers. Both patients and controls were randomly assigned to two different experimental groups: the first group underwent evaluation of ICF, while in the second group we assessed SICI and LICI. All these measures were assessed by using three different suprathreshold intensities of the TS (110%, 130% and 150% of the resting motor threshold, RMT). Interstimulus intervals (ISIs) of 10 ms were used for testing ICF, while SICI and LICI were carried out by using 2 ms and 100 ms ISIs respectively. All migraine patients underwent the experimental protocol while in the interictal pain-free state.

RESULTS: A main finding of the study was that an increased ICF could be seen in migraineurs as compared to the healthy subjects only by using a 110% intensity of the TS. Instead, no significant differences were observed between patients and controls as regards both measures of intracortical inhibition.

CONCLUSION: We show that hyperresponsivity of the glutamatergic intracortical circuits can be detected in the migraine motor cortex only by applying a low suprathreshold intensity of stimulation. Our results strengthen the notion that, to be reliable, the assessment of cortical excitability in migraine should always include evaluation of the cortical response to different stimulation intensities.

CHRONIC PAIN

**Prevalence and profile of High Impact Chronic Pain in the United States.**

Pitcher MH1, Von Korff M2, Bushnell MC3, Porter L4.


The multidimensional nature of chronic pain is not reflected by definitions based solely on pain duration, resulting in high prevalence estimates limiting effective policy development. The newly proposed concept of High Impact Chronic Pain (HICP) incorporates both disability and pain duration to identify a more severely impacted portion of the chronic pain population, yet remains uncharacterized at the population level. As such, we used the 2011 National Health Interview Survey (NHIS; n=15,670) to (i) assess the likelihood of disability in the overall chronic pain population, (ii) to estimate the prevalence of HICP, and (iii) to characterize the disability, health status and health care use profile of this population in the United States. Overall, chronic pain, defined as pain experienced on most or every day in the last three months, was strongly associated with an increased risk of disability after controlling for other chronic health conditions (OR=4.43, CI=3.73-5.26), where disability was more likely in those with chronic pain than in those with stroke or kidney failure, among others. HICP affected 4.8% of the U.S. adult population, or approximately 10.6 million individuals in 2011. The HICP population reported more severe pain, mental health and cognitive impairments than persons with chronic pain without disability, and was also more likely to report worsening health, more difficulty with self-care and higher health care use. HICP clearly represents a more severely impacted portion of the chronic pain population. Understanding this heterogeneity will contribute to developing more effective legislation promoting safe and cost-effective approaches to prevention and treatment of chronic pain.

PERSPECTIVE: High Impact Chronic Pain is a powerful new classification that differentiates those with debilitating chronic pain from those with less impactful chronic pain. By addressing the multi-dimensionality of chronic pain, this classification will improve clinical practice, research and the development of effective health policy.
CHRONIC PAIN (Continued)

**The Pain Course: 12 and 24 month outcomes from a randomised controlled trial of an internet-delivered pain management program provided with different levels of clinician support.**

Dear BE¹, Gandy M², Karin E², Fogliati R², Fogliati VJ², Staples LG², Wootton BM³, Sharpe L⁴, Titov N².


Little is known about the long-term outcomes of emerging internet-delivered pain management programs. The current study reports the 12-month and 24-month follow-up data from a randomised controlled trial (n = 490) of an internet-delivered pain management program, the Pain Course. The initial results of the trial to 3-month follow-up have already been reported elsewhere. Significant improvements in disability, depression, anxiety and pain levels across three treatment groups receiving different levels of clinician support, compared with a treatment-as-usual control. No marked or significant differences were found between the treatment groups at either post-treatment or 3-month follow-up. The current study obtained long term follow-up data from 78% and 79% of participants (n = 397) at 12-month and 24-month follow-up, respectively. Clinically significant reductions (average % reduction; Cohen's d effect sizes) were maintained at 12 and 24-month follow-up for disability (avg. reduction ≥ 27%; ds ≥ 0.67), depression (avg. reduction ≥ 36%; ds ≥ 0.80), anxiety (avg. reduction ≥ 38%; ds ≥ 0.66) and average pain levels (avg. reduction ≥ 21%; ds ≥ 0.67). No marked or consistent differences were found between the three treatment groups. These findings suggest the outcomes of internet-delivered programs may be maintained over the long-term.

**PERSPECTIVE:** This article presents the long-term outcome data of an established internet-delivered pain management program for adults with chronic pain. The clinical improvements observed during the program were found to be maintained at 12 and 24-month follow-up. This indicates that these programs can have lasting clinical effects.

**Mindfulness, selfcompassion, and depressive symptoms in chronic pain: The role of pain acceptance.**

Carvalho SA¹, Gillanders D², Palmeira L¹, Pinto-Gouveia J¹, Castilho P¹.


OBJECTIVE(S): The aim of this study was to test a theory driven model in which pain acceptance (both pain willingness [PW] and activity engagement [AE]) mediates the relationships of mindfulness and selfcompassion with depressive symptoms, while controlling for pain intensity.

METHODS: A path analysis was conducted using AMOS software to test a meditational model in a sample of women with chronic musculoskeletal pain (N = 231).

RESULTS: Participants with higher levels of mindful awareness and selfcompassion presented lower levels of pain intensity and depressive symptoms, and higher levels of AE. PW did not significantly correlate with any variable in study. The mediation analysis showed that AE mediated the relationship between selfcompassion and depressive symptoms, independently from pain intensity.

CONCLUSIONS: These findings seem to corroborate the hypothesis that selfcompassion is rooted in a motivational system, as it seems to correlate with less depressive symptoms through increasing the engagement with valued actions despite experiencing pain.
CHRONIC PAIN (Continued)

What Do Providers Want from a Pain Screening Measure Used in Daily Practice?
Giannitrapani KF1, Day RT1, Azarfar A1, Ahluwalia SC2, Dobscha S3,4, Lorenz KA1,2,5.

Objectives: We aimed to understand providers’ experiences and preferences regarding several brief pain screening measures.

Methods: We collected two waves of data for this analysis. Wave one: We conducted nine focus groups with multidisciplinary Department of Veterans Affairs (VA) providers. Wave two: To understand an emergent theme in wave one, we conducted 15 telephone interviews with prescribing providers where we used a semistructured guide comparing screening measures currently used in VA practices. Using content analysis of the wave two interviews, we evaluated providers’ perceptions of important aspects of brief pain screening measures and reported emergent themes.

Results: Five emergent themes underlie providers’ perceptions of the utility of brief pain screening measures: 1) item abstractness: how bounded and concrete a patient's interpretation of an individual item is; 2) item distinctness: belief in the patient's ability to differentiate between the meaning of various items in a pain measure; 3) item anchoring: presence of a description under each response option making the meaning explicit; 4) item look-back period: the period of time over which patients are asked to remember and comment on their pain; 5) parsimony: identifying the shortest and simplest approach possible to acquire desired information.

Conclusions: Overly complex or adaptive screening tools may include information that is ultimately not used by providers. Conversely, overly simplistic pain screening tools may omit information that helps providers understand the impact of pain on patients’ lives. As pain is nuanced, complex, and subjective, all screening measures exhibit some limitations. No single pain measure serves all chronic pain patients, and specific contexts or settings may warrant additional specific items.

OTHER RESEARCH OF INTEREST

Association between physical exercise and mental health in 1·2 million individuals in the USA between 2011 and 2015: a cross-sectional study.
Chekroud SR1, Gueorguieva R2, Zheutlin AB3, Paulus M4, Krumholz HM5, Krystal JH6, Chekroud AM7.

BACKGROUND: Exercise is known to be associated with reduced risk of all-cause mortality, cardiovascular disease, stroke, and diabetes, but its association with mental health remains unclear. We aimed to examine the association between exercise and mental health burden in a large sample, and to better understand the influence of exercise type, duration, frequency, and intensity.

METHODS: In this cross-sectional study, we analysed data from 1 237 194 people aged 18 years or older in the USA from the 2011, 2013, and 2015 Centers for Disease Control and Prevention Behavioral Risk Factors Surveillance System survey. We compared the number of days of bad self-reported mental health between individuals who exercised and those who did not, using an exact non-parametric matching procedure to balance the two groups in terms of age, race, gender, marital status, income, education level, body-mass index category, self-reported physical health, and previous diagnosis of depression. We examined the effects of exercise type, duration, frequency, and intensity using regression methods adjusted for potential confounders, and did multiple sensitivity analyses.

FINDINGS: Individuals who exercised had 1·49 (43·2%) fewer days of poor mental health in the past month than individuals who did not exercise but were otherwise matched for several physical and sociodemographic characteristics (W=7·42 × 10^10, p<2·2 × 10^-16). All exercise types were associated with a lower mental health burden (minimum reduction of 11·8% and maximum reduction of 22·3%) than not exercising (p<2·2 × 10^-16 for all exercise types). The largest associations were seen for popular team sports (22·3% lower), cycling (21·6% lower), and aerobic and gym activities (20·1% lower), as well as durations of 45 min and frequencies of three to five times per week.

INTERPRETATION: In a large US sample, physical exercise was significantly and meaningfully associated with self-reported mental health burden in the past month. More exercise was not always better. Differences as a function of exercise were large relative to other demographic variables such as education and income. Specific types, durations, and frequencies of exercise might be more effective clinical targets than others for reducing mental health burden, and merit interventional study.

FUNDING: Cloud computing resources were provided by Microsoft.

Debra L. Blackwell, Ph.D., and Tainya C. Clarke, Ph.D., M.P.H.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES Centers for Disease Control and Prevention National Center for Health Statistics, National Health Statistics Reports, Number 112, June 28, 2018

Objective—This report presents national and state-level age-adjusted estimates of percentages of U.S. adults aged 18–64 who met the 2008 federal guidelines for both aerobic and muscle-strengthening activities during leisure-time physical activity (LTPA) in 2010–2015, by sex and work status (working compared with nonworking). State variation in work status, health status and difficulty in physical functioning, and occupational distributions for men and women were also considered.

Methods—The 2008 physical activity guidelines recommend muscle-strengthening activities at least twice weekly, with either moderate-intensity aerobic physical activity for at least 150 minutes per week, vigorous-intensity aerobic physical activity for at least 75 minutes per week, or an equivalent combination. Percentage estimates are based on pooled data from the 2010–2015 National Health Interview Survey for all 50 states and the District of Columbia. A series of maps show how state estimates for meeting the guidelines during LTPA differ by sex and current work status.

Results—Nationally, 22.9% of U.S. adults aged 18–64 met the guidelines for both aerobic and muscle-strengthening activities during LTPA in 2010–2015. However, the extent to which adults met these guidelines varied by state, sex, and current work status. Fourteen states and the District of Columbia had significantly higher percentages of adults meeting the guidelines through LTPA than the national average, while 13 states had percentages that were significantly below the national average. The percentage of men who met the guidelines through participation in LTPA varied from 17.7% in South Dakota to 40.3% in the District of Columbia, with the national average being 27.2%. Among women, percentages varied from 9.7% in Mississippi to 31.5% in Colorado, with the national average for women being 18.7%. Percentages meeting the guidelines among men were less regionally concentrated than among women, especially with respect to exceeding the guidelines.

Traumatic Brain Injury, Sleep Quality, and Suicidal Ideation in Iraq/Afghanistan Era Veterans.

DeBeer BB1, Kimbrel NA, Mendoza C, Davidson D, Meyer EC, La Bash H, Gulliver SB, Morissette SB.


The objective of this study was to test the hypothesis that sleep quality mediates the association between traumatic brain injury (TBI) history and current suicidal ideation. Measures of TBI history, sleep quality, and suicidal ideation were administered to 130 Iraq/Afghanistan veterans. As expected, sleep quality mediated the effect of TBI history on current suicidal ideation (indirect effect, 0.0082; 95% confidence interval, 0.0019-0.0196), such that history of TBI was associated with worse sleep quality, which was, in turn, associated with increased suicidal ideation. These findings highlight the importance of assessing TBI history and sleep quality during suicide risk assessments for veterans.
Background: Patients with inflammatory bowel disease (IBD) often suffer from rheumatic manifestations, including inflammatory back disorders. The prevalence of these disorders late in the course of IBD is poorly investigated. The aim of this study was to estimate the prevalence of inflammatory back disorders in patients with IBD 20 years after diagnosis, and to investigate possible associations with IBD severity, HLA-B27, and the NOD2 genotype.

Methods: A population-based cohort [the IBSEN study] was followed prospectively for 20 years. Information covering IBD activity and rheumatic diseases was collected at the regular follow-ups. HLA-B27 and NOD2 were analysed as present or absent.

Results: At 20 years, 599 members of the original cohort were alive, of whom 470 [78.5%] were investigated [314 ulcerative colitis and 156 Crohn's disease patients]. Ankylosing spondylitis was diagnosed in 21 patients [4.5%], axial spondyloarthritis was diagnosed in 36 patients [7.7%], and inflammatory back pain was diagnosed in 54 patients [11.5%]. Chronic back pain [back pain > 3 months] was present in 220 patients [46.8%]. HLA-B27 was associated with ankylosing spondylitis, axial spondyloarthritis, and inflammatory back pain, whereas no significant association was found for NOD2. A more chronic IBD course was associated with axial spondyloarthritis.

Conclusions: Our data revealed a high prevalence of ankylosing spondylitis, axial spondyloarthritis, and inflammatory back pain 20 years after the IBD diagnosis. HLA-B27 but not NOD-2 was a predisposing factor for the inflammatory back disorders in IBD patients. Axial spondyloarthritis was associated with a more chronic active IBD disease course.