GULF WAR ILLNESS

No Updates this Week for Gulf War Illness or Chronic Multisymptom Illness.

CHRONIC FATIGUE SYNDROME

Dutch Health Council Advisory Report on Myalgic Encephalomyelitis and Chronic Fatigue Syndrome: Taking the Wrong Turn.

Twisk F[1].

Diagnostics (Basel). **2018 May 16**;8(2). pii: E34. doi: 10.3390/diagnostics8020034. PMID: 29772739.

Recently, the Dutch Health Council published their advisory report on Myalgic Encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS) which is meant to determine the medical policy with regard to ME in the Netherlands. The Health Council briefly discusses several diagnostic criteria and proposes to use new diagnostic criteria for "ME/CFS" in research and clinical practice in the future. The advisory report then summarizes organic abnormalities observed in the last decades and concludes that "ME/CFS" is a "serious, chronic, multisystem disease". According to the Health Council there are no curative treatments for "ME/CFS", due to lack of knowledge, but specific medication could bring symptomatic relief. The Health Council recommends conducting more research, to (re)educate medical professionals about "ME/CFS", to appoint three academic expertise centres, which will install a care network for patients, and to fairly judge the limitations (disability) of patients when they apply for a disability income, medical aid and care. The advisory report was welcomed by many patients, because it puts an end to the dominance of the (bio)psychosocial explanatory model and seems to offer a perspective of improving the situation of patients. However, the starting point of the advisory report, a new definition of "ME/CFS", will have serious (long-lasting) consequences for patients and researchers.

Poor self-reported sleep quality and health-related quality of life in patients with chronic fatigue syndrome/myalgic encephalomyelitis.

Castro-Marrero J[1], Zaragozá MC[1,2], González-Garcia S[1], Aliste L[1], Sáez-Francàs N[3], Romero O[4,5], Ferré A[4,5], Fernández de Sevilla T[1], Alegre J[1].

J Sleep Res. **2018 May 16**:e12703. doi: 10.1111/jsr.12703. PMID: 29770505. [Epub ahead of print]

Non-restorative sleep is a hallmark symptom of chronic fatigue syndrome/myalgic encephalomyelitis. However, little is known about self-reported sleep disturbances in these subjects. This study aimed to assess the self-reported sleep quality and its impact on quality of life in a Spanish community-based chronic fatigue syndrome/myalgic encephalomyelitis cohort. A prospective cross-sectional cohort study was conducted in 1,455 Spanish chronic fatigue syndrome/myalgic encephalomyelitis patients. Sleep quality, fatigue, pain, functional capacity impairment, psychopathological status, anxiety/depression and health-related quality of life were assessed using validated subjective measures. The frequencies of muscular, cognitive, neurological, autonomic and immunological symptom clusters were above 80%. High scores were recorded for pain, fatigue, psychopathological status, anxiety/depression, and low scores for functional capacity and quality of life, all of which correlated significantly (all $p < 0.01$) with quality of sleep as measured by the Pittsburgh Sleep Quality Index. Multivariate regression analysis showed that after adjusting for age and gender, the pain intensity (odds ratio, 1.11; $p <0.05$), psychopathological status (odds ratio, 1.85; $p < 0.001$), fibromyalgia (odds ratio, 1.39; $p < 0.05$), severe autonomic dysfunction (odds ratio, 1.72; $p < 0.05$), poor functional capacity (odds ratio, 0.98; $p < 0.05$) and quality of life (odds ratio, 0.96; both $p < 0.001$) were significantly associated with poor sleep quality. These findings suggest that this large chronic fatigue syndrome/myalgic encephalomyelitis sample presents poor sleep quality, as assessed by the Pittsburgh Sleep Quality Index, and that this poor sleep quality is associated with many aspects of quality of life.

CHRONIC FATIGUE SYNDROME (Continued)

Childhood sleep and adolescent chronic fatigue syndrome (CFS/ME): evidence of associations in a UK birth cohort.

Collin SM[1], Norris T[2], Gringras P[3], Blair PS[4], Tilling K[4], Crawley E[5].

Sleep Med. **2018 Jun**;46:26-36. doi: 10.1016/j.sleep.2018.01.005. PMID: 29773208. Epub 2018 Jan 31.

OBJECTIVE/BACKGROUND: Sleep abnormalities are characteristic of chronic fatigue syndrome (CFS, also known as 'ME'), however it is unknown whether sleep might be a causal risk factor for CFS/ME.

PATIENTS/METHODS: We analysed data from the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort. We describe sleep patterns of children aged 6 months to 11 years, who were subsequently classified as having (or not having) 'chronic disabling fatigue' (CDF, a proxy for CFS/ME) between the ages 13 and 18 years, and we investigated the associations of sleep duration at age nine years with CDF at age 13 years, as well as sleep duration at age 11 years with CDF at age 16 years.

RESULTS: Children who had CDF during adolescence had shorter night-time sleep duration from 6 months to 11 years of age, and there was strong evidence that difficulties in going to sleep were more common in children who subsequently developed CDF. The odds of CDF at age 13 years were 39% lower (odds ratio (OR) = 0.61, 95% CI = 0.43, 0.88) for each additional hour of night-time sleep at age nine years, and the odds of CDF at age 16 years were 51% lower (OR = 0.49, 95% CI = 0.34, 0.70) for each additional hour of night-time sleep at age 11 years. Mean night-time sleep duration at age nine years was 13.9 (95% CI = 3.75, 24.0) minutes shorter among children who developed CDF at age 13 years, and sleep duration at age 11 years was 18.7 (95% CI = 9.08, 28.4) minutes shorter among children who developed CDF at age 16 (compared with children who did not develop CDF at 13 and 16 years, respectively).

CONCLUSIONS: Children who develop chronic disabling fatigue in adolescence have shorter night-time sleep duration throughout early childhood, suggesting that sleep abnormalities may have a causal role in CFS/ME or that sleep abnormalities and CFS/ME are associated with a common pathophysiological cause.

HEADACHE and MIGRAINE

FDA approves novel preventive treatment for migraine

U.S. Food & Drug Administration, **May 17, 2018**.

The U.S. Food and Drug Administration today approved Aimovig (erenumab-aooe) for the preventive treatment of migraine in adults. The treatment is given by once-monthly self-injections. Aimovig is the first FDA-approved preventive migraine treatment in a new class of drugs that work by blocking the activity of calcitonin gene-related peptide, a molecule that is involved in migraine attacks.

“Aimovig provides patients with a novel option for reducing the number of days with migraine,” said Eric Bastings, M.D., deputy director of the Division of Neurology Products in the FDA’s Center for Drug Evaluation and Research. “We need new treatments for this painful and often debilitating condition.”

Patients often describe migraine headache pain as an intense pulsing or throbbing pain in one area of the head. Additional symptoms include nausea and/or vomiting and sensitivity to light and sound. Approximately one-third of affected individuals can predict the onset of a migraine because it is preceded by an aura – transient sensory or visual disturbances that appear as flashing lights, zig-zag lines or a temporary loss of vision. People with migraine tend to have recurring attacks triggered by a number of different factors, including stress, hormonal changes, bright or flashing lights, lack of food or sleep and diet. Migraine is three times more common in women than in men and affects more than 10 percent of people worldwide.

The effectiveness of Aimovig for the preventive treatment of migraine was evaluated in three clinical trials. The first study included 955 participants with a history of episodic migraine and compared Aimovig to placebo. Over the course of six months, Aimovig-treated patients experienced, on average, one to two fewer monthly migraine days than those on placebo. The second study included 577 patients with a history of episodic migraine and compared Aimovig to placebo. Over the course of three months, Aimovig-treated patients experienced, on average, one fewer migraine day per month than those on placebo. The third study evaluated 667 patients with a history of chronic migraine and compared Aimovig to placebo. In that study, over the course of three months, patients treated with Aimovig experienced, on average, 2 ½ fewer monthly migraine days than those receiving placebo.

The most common side effects that patients in the clinical trials reported were injection site reactions and constipation.

The FDA granted the approval of Aimovig to Amgen Inc.

HEADACHE and MIGRAINE (Continued)

Effect of Fremanezumab Compared With Placebo for Prevention of Episodic Migraine. A Randomized Clinical Trial

David W. Dodick, MD[1]; Stephen D. Silberstein, MD[2]; Marcelo E. Bigal, MD, PhD[3]; et al Paul P. Yeung, MD, MPH[3]; Peter J. Goadsby, MD, PhD[4]; Tricia Blankenbiller, MA[3]; Melissa Grozinski-Wolff[3]; Ronghua Yang, PhD[3]; Yuju Ma, MS[3]; Ernesto Aycardi, MD[3]

JAMA, Original Investigation, **May 15, 2018**;319(19):1999-2008. doi:10.1001/jama.2018.4853

Key Points

Question: Is the monoclonal antibody fremanezumab effective in preventing episodic migraine?

Findings: In this randomized clinical trial that included 875 adults with episodic migraine in whom multiple medication classes had not previously failed, fremanezumab compared with placebo resulted in significantly fewer monthly migraine days with monthly dosing (–1.5 days) and with a single higher dose at baseline (–1.3 days) over 12 weeks.

Meaning: Fremanezumab as a preventive treatment for episodic migraine reduced the mean number of monthly migraine days over a 12-week period compared with placebo. Further research is needed to assess effectiveness against other preventive medications and in patients in whom multiple preventive drug classes have failed and to determine long-term safety and efficacy.

Abstract

Importance: Fremanezumab, a fully humanized monoclonal antibody that targets calcitonin gene-related peptide, may be effective for treating episodic migraine.

Objective: To assess the efficacy of fremanezumab compared with placebo for prevention of episodic migraine with a monthly dosing regimen or a single higher dose.

Design and Setting: Randomized, double-blind, placebo-controlled, parallel-group trial conducted at 123 sites in 9 countries from March 23, 2016 (first patient randomized), to April 10, 2017, consisting of a screening visit, 28-day pretreatment period, 12-week treatment period, and final evaluation at week 12.

Participants: Study participants were aged 18 to 70 years with episodic migraine (6-14 headache days, with at least 4 migraine days, during 28-day pretreatment period). Patients who had previous treatment failure with 2 classes of migraine-preventive medication were excluded.

Interventions: Patients were randomized 1:1:1 to receive subcutaneous monthly dosing of fremanezumab (n = 290; 225 mg at baseline, week 4, and week 8); a single higher dose of fremanezumab, as intended to support a quarterly dose regimen (n = 291; 675 mg of fremanezumab at baseline; placebo at weeks 4 and 8); or placebo (n = 294; at baseline, week 4, and week 8).

Main Outcomes and Measures: The primary end point was mean change in mean number of monthly migraine days during the 12-week period after the first dose.

Results: Among 875 patients who were randomized (mean age, 41.8 [SD, 12.1] years; 742 women [85%]), 791 (90.4%) completed the trial. From baseline to 12 weeks, mean migraine days per month decreased from 8.9 days to 4.9 days in the fremanezumab monthly dosing group, from 9.2 days to 5.3 days in the fremanezumab single-higher-dose group, and from 9.1 days to 6.5 days in the placebo group. This resulted in a difference with monthly dosing vs placebo of –1.5 days (95% CI, –2.01 to –0.93 days; $P < .001$) and with single higher dosing vs placebo of –1.3 days (95% CI, –1.79 to –0.72 days; $P < .001$). The most common adverse events that led to discontinuation were injection site erythema (n = 3), injection site induration (n = 2), diarrhea (n = 2), anxiety (n = 2), and depression (n = 2).

Conclusions and Relevance: Among patients with episodic migraine in whom multiple medication classes had not previously failed, subcutaneous fremanezumab, compared with placebo, resulted in a statistically significant 1.3- to 1.5-day reduction in the mean number of monthly migraine days over a 12-week period. Further research is needed to assess effectiveness against other preventive medications and in patients in whom multiple preventive drug classes have failed and to determine long-term safety and efficacy.

Trial Registration: clinicaltrials.gov Identifier: NCT02629861

HEADACHE and MIGRAINE (Continued)

The development of a mouse model of mTBI-induced post-traumatic migraine, and identification of the delta opioid receptor as a novel therapeutic target.

Moye LS[1], Novack ML[1], Tipton AF[1], Krishnan H[1], Pandey SC[1,2,3], Pradhan AA[1].

Cephalalgia. **2018 Jan 1**:333102418777507. doi: 10.1177/0333102418777507. PMID: 29771142. [Epub ahead of print]

Background Post-traumatic headache is the most common and long-lasting impairment observed following mild traumatic brain injury, and frequently has migraine-like characteristics. The mechanisms underlying progression from mild traumatic brain injury to post-traumatic headache are not fully understood. The aim of this study was to develop a mouse model of post-traumatic headache and identify mechanisms and novel targets associated with this disorder. Methods We combined the closed head weight-drop method and the nitroglycerin chronic migraine model. To induce mild traumatic brain injury, a weight was dropped onto intact crania of mildly anesthetized mice, and mechanical responses to chronic-intermittent administration of nitroglycerin, a human migraine trigger, were determined at multiple time points post-injury. Results Low dose nitroglycerin (0.1 mg/kg) evoked acute periorbital and hind paw allodynia in both mild traumatic brain injury and sham animals. However, only mild traumatic brain injury mice developed chronic hypersensitivity to low dose nitroglycerin. Migraine medications, sumatriptan and topiramate, inhibited post-traumatic headache-associated allodynia. In addition, the delta opioid receptor agonist, SNC80, also blocked post-traumatic headache-associated allodynia. Finally, we examined the expression of calcitonin gene-related peptide within this model and found that it was increased in trigeminal ganglia two weeks post-mild traumatic brain injury. Conclusions Overall, we have established a mouse model of post-traumatic headache and identified the delta opioid receptor as a novel therapeutic target for this disorder.

Double-blind placebo-controlled randomized clinical trial of ginger (Zingiber officinale Rosc.) addition in migraine acute treatment.

Martins LB[1], Rodrigues AMDS[1], Rodrigues DF[1], Dos Santos LC[1], Teixeira AL[2], Ferreira AVM[1].

Cephalalgia. **2018 Jan 1**:333102418776016. doi: 10.1177/0333102418776016. PMID: 29768938. [Epub ahead of print]

Background Previous studies have demonstrated the analgesic effects of ginger in different conditions, but evidence about its efficacy in migraine treatment is scarce. Objective This study aimed to evaluate the potential of ginger to improve acute migraine as an add-on strategy to standard treatment. Methods A double-blind placebo-controlled randomized clinical trial in the emergency room of a general hospital was conducted. Patients who sought medical care at the time of migraine attack were enrolled in this study. Only adults with episodic migraine (one to six migraine attacks per month) with or without aura were included. Sixty participants were randomized into two groups in which they received 400 mg of ginger extract (5% active ingredient) or placebo (cellulose), in addition to an intravenous drug (100 mg of ketoprofen) to treat the migraine attack. Patients filled a headache diary before, 0.5 h, 1 h, 1.5 h and 2 h after the medication. Pain severity, functional status, migraine symptoms and treatment satisfaction were also recorded. Results Patients treated with ginger showed significantly better clinical response after 1 h ($p = 0.04$), 1.5 h ($p = 0.01$) and 2 h ($p = 0.04$). Furthermore, ginger treatment promoted reduction in pain and improvement on functional status at all times assessed. Conclusions The addition of ginger to non-steroidal anti-inflammatory drugs may contribute to the treatment of migraine attack. This trial is registered at ClinicalTrials.gov (NCT02568644).

CHRONIC PAIN

Exposure and CBT for chronic back pain: An RCT on differential efficacy and optimal length of treatment.

Glombiewski JA[1], Holzapfel S[1], Riecke J[1], Vlaeyen JWS[2], de Jong J[3], Lemmer G[4], Rief W[1].

J Consult Clin Psychol. **2018 Jun**;86(6):533-545. doi: 10.1037/ccp0000298. PMID: 29781651.

OBJECTIVE: Our aim was to establish whether Exposure, a specialized tailored treatment for chronic low back pain, has any advantages over cognitive-behavioral therapy (CBT) among individuals with high fear-avoidance levels. Second, we planned to compare short and long versions of Exposure. Third, we aimed to investigate whether Exposure can be delivered in an outpatient psychological setting.

METHOD: A total of 88 Caucasian participants (55% women) were randomized to three different psychological treatment conditions, Exposure-long, Exposure-short, and CBT. All participants were suffering from chronic pain and elevated levels of pain-related anxiety and disability. The primary outcomes were disability (assessed using two different questionnaires, QBPDS and PDI) and average pain intensity; secondary outcomes included pain-related anxiety, psychological flexibility, coping strategies, and depression. Assessments took place at pretreatment, midtreatment, posttreatment, and 6-month follow-up.

RESULTS: Exposure was more effective than CBT at reducing movement-related disability assessed with the QBPDS. Exposure and CBT did not differ in reduction of pain intensity or disability assessed using the PDI. Exposure-short outperformed Exposure-long after 10 sessions, meaning that individuals improved faster when they were offered fewer sessions. Exposure could be safely delivered in the psychological setting. Concerning secondary outcomes, Exposure led to greater improvements in psychological flexibility relative to CBT. CBT was more effective than Exposure at enhancing coping strategies. In Exposure, significantly more participants dropped out.

CONCLUSIONS: Although being more challenging to patients, Exposure is an effective treatment, which can be delivered in a psychological treatment setting and should be offered as a short-term treatment. (PsycINFO Database Record

TRIAL REGISTRATION: ClinicalTrials.gov NCT01484418.

Brain Correlates of Continuous Pain in Rheumatoid Arthritis as Measured by Pulsed Arterial Spin Labeling.

Lee YC[1], Fine A[1], Protsenko E[2], Massarotti E[1], Edwards RR[3], Mawla I[2], Napadow V[2], Loggia ML[2].

Arthritis Care Res (Hoboken). **2018 May 21**. doi: 10.1002/acr.23601. PMID: 29781581. [Epub ahead of print]

OBJECTIVE: Central nervous system pathways involving pain modulation shape the pain experience in patients with chronic pain. Our objectives were to understand the mechanisms underlying pain in rheumatoid arthritis (RA) and identify brain signals that may serve as imaging markers for developing targeted treatments for RA pain.

METHODS: Subjects with RA and matched controls underwent functional magnetic resonance imaging, using pulsed arterial spin labeling (pASL). The imaging conditions included: 1) resting state, 2) low intensity stimulus and 3) high intensity stimulus. Stimuli consisted of mechanical pressure applied to metacarpophalangeal (MCP) joints with an automated cuff inflator. The low intensity stimulus was 30 mmHg. The high intensity stimulus was the amount of pressure required to achieve 40/100 pain intensity for each RA patient, with the same amount of pressure given to the matched control.

RESULTS: Among RA patients, regional cerebral blood flow (rCBF) in medial frontal cortex (MFC) and dorsolateral prefrontal cortex increased during both low and high pressure stimuli. No rCBF changes were noted for pain-free controls. In region of interest analyses among RA patients, baseline rCBF in MFC was negatively correlated with pressure required for the high intensity stimulus ($p<0.01$) and positively correlated with pain induced by the low intensity stimulus ($p<0.05$). Baseline rCBF also marginally correlated with disease activity ($p=0.05$). rCBF during high pain was positively correlated with pain severity and interference ($p's<0.05$).

CONCLUSION: In response to clinically-relevant joint pain evoked by MCP pressure, neural processing in MFC increases and is directly associated with clinical pain in RA. This article is protected by copyright. All rights reserved.

CHRONIC PAIN (Continued)

N-methyl D-aspartate receptor subtype 2B antagonist, Ro 25-6981, attenuates neuropathic pain by inhibiting postsynaptic density 95 expression.

Huang LE[1], Guo SH[1], Thitiseranee L[2], Yang Y[3], Zhou YF[1], Yao YX[4].

Sci Rep. **2018 May 18**;8(1):7848. doi: 10.1038/s41598-018-26209-7. PMID: 29777135.

Postsynaptic density-95 (PSD-95) is a synaptic scaffolding protein that plays a crucial role in the development of neuropathic pain. However, the underlying mechanism remains unclear. To address the role of PSD-95 in N-methyl-D-aspartate receptor subtype 2B (NR2B) -mediated chronic pain, we investigated the relationship between PSD-95 activation and NR2B function in the spinal cord, by using a rat model of sciatic nerve chronic constriction injury (CCI). We demonstrate that the expression levels of total PSD-95 and cAMP response element binding protein (CREB), as well as phosphorylated NR2B, PSD-95, and CREB, in the spinal dorsal horn, and the interaction of NR2B with PSD-95 were increased in the CCI animals. Intrathecal injection of the selective NR2B antagonist Ro 25-6981 increased paw withdrawal latency, in a thermal pain assessment test. Moreover, repeated treatment with Ro 25-6981 markedly attenuated the thermal hypersensitivity, and inhibited the CCI-induced upregulation of PSD-95 in the spinal dorsal horn. Furthermore, intrathecal injection of the PSD-95 inhibitor strikingly reversed the thermal and mechanical hyperalgesia. Our results suggest that blocking of NR2B signaling in the spinal cord could be used as a therapeutic candidate for treating neuropathic pain.

Posttraumatic stress disorder and chronic pain are associated with opioid use disorder: Results from a 2012-2013 American nationally representative survey.

Bilevicius E[1], Sommer JL[1], Asmundson GJG[2], El-Gabalawy R[3].

Drug Alcohol Depend. **2018 May 7**;188:119-125. doi: 10.1016/j.drugalcdep.2018.04.005. PMID: 29775955. [Epub ahead of print]

BACKGROUND: Chronic pain conditions and posttraumatic stress disorder (PTSD) commonly co-occur and are associated with opioid use disorder (OUD). The aims of this paper were to identify prevalence estimates of OUD among individuals with and without PTSD and assess independent and combined contributions of PTSD and chronic pain conditions on OUD in a nationally representative sample.

METHODS: Data were extracted from 36,309 individuals from the 2012-2013 National Epidemiologic Survey on Alcohol and Related Conditions. Past-year PTSD and OUD were assessed using the Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-5 edition. Respondents reported physician-confirmed, past-year chronic pain conditions, categorized into musculoskeletal pain (e.g., arthritis), digestive pain (e.g., pancreatitis), and nerve pain (e.g., reflex sympathetic dystrophy). We examined the weighted prevalence of OUD among those with and without PTSD. Multiple logistic regressions examined the association between PTSD and chronic pain conditions on OUD.

RESULTS: The prevalence of OUD was higher among those with PTSD than those without. Comorbid PTSD/musculoskeletal pain and PTSD/nerve pain conditions were associated with increased odds of OUD, compared to those with neither PTSD nor chronic pain conditions. Digestive pain conditions were not associated with OUD. Comorbid PTSD/musculoskeletal pain conditions demonstrated an additive relationship on OUD compared to musculoskeletal pain conditions and PTSD alone.

CONCLUSIONS: Results reveal that musculoskeletal pain and nerve pain conditions are associated with increased odds of OUD, but only musculoskeletal pain conditions display an additive relationship on OUD when combined with PTSD. These findings have implications for opioid management and screening among those with comorbid conditions.

CHRONIC PAIN (Continued)

Classification and characterisation of brain network changes in chronic back pain: A multicenter study.

Mano H[#1], Kotecha G[#2], Leibnitz K[1], Matsubara T[3], Nakae A[4,5], Shenker N[2], Shibata M[4], Voon V[6], Yoshida W[7], Lee M[6], Yanagida T[1], Kawato M[7], Rosa MJ[8,9], Seymour B[1,5,7,10].

Wellcome Open Res. **2018 Mar 1**;3:19. doi: 10.12688/wellcomeopenres.14069.1. PMCID: PMC5930551. PMID: 29774244. eCollection 2018.

Background. Chronic pain is a common, often disabling condition thought to involve a combination of peripheral and central neurobiological factors. However, the extent and nature of changes in the brain is poorly understood.

Methods. We investigated brain network architecture using resting-state fMRI data in chronic back pain patients in the UK and Japan (41 patients, 56 controls), as well as open data from USA. We applied machine learning and deep learning (conditional variational autoencoder architecture) methods to explore classification of patients/controls based on network connectivity. We then studied the network topology of the data, and developed a multislice modularity method to look for consensus evidence of modular reorganisation in chronic back pain.

Results. Machine learning and deep learning allowed reliable classification of patients in a third, independent open data set with an accuracy of 63%, with 68% in cross validation of all data. We identified robust evidence of network hub disruption in chronic pain, most consistently with respect to clustering coefficient and betweenness centrality. We found a consensus pattern of modular reorganisation involving extensive, bilateral regions of sensorimotor cortex, and characterised primarily by negative reorganisation - a tendency for sensorimotor cortex nodes to be less inclined to form pairwise modular links with other brain nodes. In contrast, intraparietal sulcus displayed a propensity towards positive modular reorganisation, suggesting that it might have a role in forming modules associated with the chronic pain state.

Conclusion. The results provide evidence of consistent and characteristic brain network changes in chronic pain, characterised primarily by extensive reorganisation of the network architecture of the sensorimotor cortex.

OTHER RESEARCH OF INTEREST

Association of disrupted circadian rhythmicity with mood disorders, subjective wellbeing, and cognitive function: a cross-sectional study of 91 105 participants from the UK Biobank.

Lyall LM[1], Wyse CA[2], Graham N[3], Ferguson A[3], Lyall DM[3], Cullen B[3], Celis Morales CA[4], Biello SM[5], Mackay D[3], Ward J[3], Strawbridge RJ[6], Gill JMR[4], Bailey MES[7], Pell JP[3], Smith DJ[3].

Lancet Psychiatry. **2018 May 15**. pii: S2215-0366(18)30139-1. doi: 10.1016/S2215-0366(18)30139-1. PMID: 29776774. [Epub ahead of print]

BACKGROUND: Disruption of sleep and circadian rhythmicity is a core feature of mood disorders and might be associated with increased susceptibility to such disorders. Previous studies in this area have used subjective reports of activity and sleep patterns, but the availability of accelerometer-based data from UK Biobank participants permits the derivation and analysis of new, objectively ascertained circadian rhythmicity parameters. We examined associations between objectively assessed circadian rhythmicity and mental health and wellbeing phenotypes, including lifetime history of mood disorder.

METHODS: UK residents aged 37-73 years were recruited into the UK Biobank general population cohort from 2006 to 2010. We used data from a subset of participants whose activity levels were recorded by wearing a wrist-worn accelerometer for 7 days. From these data, we derived a circadian relative amplitude variable, which is a measure of the extent to which circadian rhythmicity of rest-activity cycles is disrupted. In the same sample, we examined cross-sectional associations between low relative amplitude and mood disorder, wellbeing, and cognitive variables using a series of regression models. Our final model adjusted for age and season at the time that accelerometry started, sex, ethnic origin, Townsend deprivation score, smoking status, alcohol intake, educational attainment, overall mean acceleration recorded by accelerometry, body-mass index, and a binary measure of childhood trauma.

FINDINGS: We included 91 105 participants with accelerometery data collected between 2013 and 2015 in our analyses. A one-quintile reduction in relative amplitude was associated with increased risk of lifetime major depressive disorder (odds ratio [OR] 1·06, 95% CI 1·04-1·08) and lifetime bipolar disorder (1·11, 1·03-1·20), as well as with greater mood instability (1·02, 1·01-1·04), higher neuroticism scores (incident rate ratio 1·01, 1·01-1·02), more subjective loneliness (OR 1·09, 1·07-1·11), lower happiness (0·91, 0·90-0·93), lower health satisfaction (0·90, 0·89-0·91), and slower reaction times (linear regression coefficient 1·75, 1·05-2·45). These associations were independent of demographic, lifestyle, education, and overall activity confounders.

INTERPRETATION: Circadian disruption is reliably associated with various adverse mental health and wellbeing outcomes, including major depressive disorder and bipolar disorder. Lower relative amplitude might be linked to increased susceptibility to mood disorders.

FUNDING: Lister Institute of Preventive Medicine.

OTHER RESEARCH OF INTEREST (Continued)

Improving risk prediction accuracy for new soldiers in the U.S. Army by adding self-report survey data to administrative data.

Bernecker SL[1,2], Rosellini AJ[3], Nock MK[1], Chiu WT[2], Gutierrez PM[4], Hwang I[2], Joiner TE[5], Naifeh JA[6], Sampson NA[2], Zaslavsky AM[2], Stein MB[7], Ursano RJ[6], Kessler RC[8].

BMC Psychiatry. **2018 Apr 3**;18(1):87. doi: 10.1186/s12888-018-1656-4. PMCID: PMC5883887. PMID: 29615005.

BACKGROUND: High rates of mental disorders, suicidality, and interpersonal violence early in the military career have raised interest in implementing preventive interventions with high-risk new enlistees. The Army Study to Assess Risk and Resilience in Servicemembers (STARRS) developed risk-targeting systems for these outcomes based on machine learning methods using administrative data predictors. However, administrative data omit many risk factors, raising the question whether risk targeting could be improved by adding self-report survey data to prediction models. If so, the Army may gain from routinely administering surveys that assess additional risk factors.

METHODS: The STARRS New Soldier Survey was administered to 21,790 Regular Army soldiers who agreed to have survey data linked to administrative records. As reported previously, machine learning models using administrative data as predictors found that small proportions of high-risk soldiers accounted for high proportions of negative outcomes. Other machine learning models using self-report survey data as predictors were developed previously for three of these outcomes: major physical violence and sexual violence perpetration among men and sexual violence victimization among women. Here we examined the extent to which this survey information increases prediction accuracy, over models based solely on administrative data, for those three outcomes. We used discrete-time survival analysis to estimate a series of models predicting first occurrence, assessing how model fit improved and concentration of risk increased when adding the predicted risk score based on survey data to the predicted risk score based on administrative data.

RESULTS: The addition of survey data improved prediction significantly for all outcomes. In the most extreme case, the percentage of reported sexual violence victimization among the 5% of female soldiers with highest predicted risk increased from 17.5% using only administrative predictors to 29.4% adding survey predictors, a 67.9% proportional increase in prediction accuracy. Other proportional increases in concentration of risk ranged from 4.8% to 49.5% (median = 26.0%).

CONCLUSIONS: Data from an ongoing New Soldier Survey could substantially improve accuracy of risk models compared to models based exclusively on administrative predictors. Depending upon the characteristics of interventions used, the increase in targeting accuracy from survey data might offset survey administration costs.

Impact of Healthy Lifestyle Factors on Life Expectancies in the US Population.

Li Y[1], Pan A[2], Wang DD[3], Liu X[3], Dhana K[4], Franco OH[5], Kaptoge S[6], Di Angelantonio E[7], Stampfer M[8], Willett WC[8], Hu FB[8].

Circulation. **2018 Apr 30**. pii: CIRCULATIONAHA.117.032047. doi: 10.1161/CIRCULATIONAHA.117.032047. PMID: 29712712. [Epub ahead of print]

Background. Americans have a shorter life expectancy compared with residents of almost all other high-income countries. We aim to estimate the impact of lifestyle factors on premature mortality and life expectancy in the US population.

Methods. Using data from the Nurses' Health Study (1980-2014; n=78 865) and the Health Professionals Follow-up Study (1986-2014, n=44 354), we defined 5 low-risk lifestyle factors as never smoking, body mass index of 18.5 to 24.9 kg/m^2, ≥30 min/d of moderate to vigorous physical activity, moderate alcohol intake, and a high diet quality score (upper 40%), and estimated hazard ratios for the association of total lifestyle score (0-5 scale) with mortality. We used data from the NHANES (National Health and Nutrition Examination Surveys; 2013-2014) to estimate the distribution of the lifestyle score and the US Centers for Disease Control and Prevention WONDER database to derive the age specific death rates of Americans. We applied the life table method to estimate life expectancy by levels of the lifestyle score.

Results. During up to 34 years of follow-up, we documented 42 167 deaths. The multivariable-adjusted hazard ratios for mortality in adults with 5 compared with zero low-risk factors were 0.26 (95% confidence interval [CI], 0.22-0.31) for all-cause mortality, 0.35 (95% CI, 0.27-0.45) for cancer mortality, and 0.18 (95% CI, 0.12-0.26) for cardiovascular disease mortality. The population-attributable risk of nonadherence to 5 low-risk factors was 60.7% (95% CI, 53.6-66.7) for all-cause mortality, 51.7% (95% CI, 37.1-62.9) for cancer mortality, and 71.7% (95% CI, 58.1-81.0) for cardiovascular disease mortality. We estimated that the life expectancy at age 50 years was 29.0 years (95% CI, 28.3-29.8) for women and 25.5 years (95% CI, 24.7-26.2) for men who adopted zero low-risk lifestyle factors. In contrast, for those who adopted all 5 low-risk factors, we projected a life expectancy at age 50 years of 43.1 years (95% CI, 41.3-44.9) for women and 37.6 years (95% CI, 35.8-39.4) for men. The projected life expectancy at age 50 years was on average 14.0 years (95% CI, 11.8-16.2) longer among female Americans with 5 low-risk factors compared with those with zero low-risk factors; for men, the difference was 12.2 years (95% CI, 10.1-14.2).

Conclusions. Adopting a healthy lifestyle could substantially reduce premature mortality and prolong life expectancy in US adults.

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