GULF WAR ILLNESS

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

CHRONIC FATIGUE SYNDROME

Impairments in cognitive performance in chronic fatigue syndrome are common, not related to co-morbid depression but do associate with autonomic dysfunction.

Robinson LJ[1], Gallagher P[2], Watson S[3], Pearce R[4], Finkelmeyer A[2], Maclachlan L[4], Newton JL[4,5].

PLoS One. **2019 Feb 5**;14(2):e0210394. doi: 10.1371/journal.pone.0210394. PMID: 30721241. eCollection 2019.

OBJECTIVES: To explore cognitive performance in chronic fatigue syndrome (CFS) examining two cohorts. To establish findings associated with CFS and those related to co-morbid depression or autonomic dysfunction.

METHODS: Identification and recruitment of participants was identical in both phases, all CFS patients fulfilled Fukuda criteria. In Phase 1 (n = 48) we explored cognitive function in a heterogeneous cohort of CFS patients, investigating links with depressive symptoms (HADS). In phase 2 (n = 51 CFS & n = 20 controls) participants with co-morbid major depression were excluded (SCID). Furthermore, we investigated relationships between cognitive performance and heart rate variability (HRV).

RESULTS: Cognitive performance in unselected CFS patients is in average range on most measures. However, 0-23% of the CFS sample fell below the 5th percentile. Negative correlations occurred between depressive symptoms (HAD-S) with Digit-Symbol-Coding (r = -.507, p = .006) and TMT-A (r = -.382, p = .049). In CFS without depression, impairments of cognitive performance remained with significant differences in indices of psychomotor speed (TMT-A: p = 0.027; digit-symbol substitution: p = 0.004; digit-symbol copy: p = 0.007; scanning: p = .034) Stroop test suggested differences due to processing speed rather than inhibition. Both cohorts confirmed relationships between cognitive performance and HRV (digit-symbol copy (r = .330, p = .018), digit-symbol substitution (r = .313, p = .025), colour-naming trials Stroop task (r = .279, p = .050).

CONCLUSION: Cognitive difficulties in CFS may not be as broad as suggested and may be restricted to slowing in basic processing speed. While depressive symptoms can be associated with impairments, co-morbidity with major depression is not itself responsible for reductions in cognitive performance. Impaired autonomic control of heart-rate associates with reductions in basic processing speed.

Post-bacterial infection chronic fatigue syndrome is not a latent infection.

Melenotte C[1], Drancourt M[2], Gorvel JP[3], Mège JL[2], Raoult D[2].

Med Mal Infect. **2019 Feb 2**. pii: S0399-077X(18)30792-3. doi: 10.1016/j.medmal.2019.01.006. PMID: 30722945. [Epub ahead of print]

Post-infectious chronic fatigue syndrome is a public health problem. Etiologies and physiopathological mechanisms are unknown. Some viruses are known to be involved in post-infectious chronic fatigue syndrome, but the role of bacterial infection is still questioned, especially in cases of post-treatment Lyme disease syndrome where subjective symptoms are regularly attributed to the presence of the dormant bacterium without scientific evidence. However, the medical experience of recalcitrant infections, relapses, and reactivations questions the role of "dormant bacteria" in asymptomatic latent infections as well as in subjective symptoms. We summarized scientific literature data on post-bacterial infection chronic fatigue syndrome, the role of dormant bacteria in latent infections, and bacterial asymptomatic carriage. Subjective symptoms described in post-infectious chronic fatigue syndromes are still misunderstood and there is no evidence suggesting that such symptoms could be related to dormant bacterial infection or carriage of viable bacteria. Psychological trauma may be part of these subjective symptoms. Post-infectious chronic fatigue syndrome could nonetheless be due to unknown microorganisms. Antibiotic treatment is not required for latent infections, except for latent syphilis and latent tuberculosis infections to prevent, after the primary infection, progression to the secondary or tertiary stage of the disease.

CHRONIC FATIGUE SYNDROME (Continued)

PACE chronic fatigue trial was properly conducted, says UK research watchdog.

Hawkes N[1].

BMJ. **2019 Feb 7**;364:l639. doi: 10.1136/bmj.l639. PMID: 30733199

The PACE trial, which compared treatments for chronic fatigue syndrome, met all the regulatory requirements of its day and exceeded transparency requirements, the Health Research Authority has concluded.

The judgment came in the form of a letter from Jonathan Montgomery, chair of the HRA, to Norman Lamb, chair of the House of Commons Science and Technology Committee. A member of the committee, Carol Monaghan, had raised the issue with Montgomery when he gave evidence on research integrity to its inquiry last year.

Although the HRA's intervention will come as a comfort to the team that led the trial and to the Medical Research Council, which funded it, it is unlikely to put to bed a longstanding campaign by activists to discredit it.

PACE was a trial led by Peter White of Queen Mary University of London that compared four treatments for chronic fatigue syndrome. Its conclusions, published in the *Lancet* in 2011, found that cognitive behavioural therapy and graded exercise therapy worked better than adaptive pacing therapy or specialist medical care.

Ever since, the trial has been the eye around which a hurricane of argument and personal vitriol has flowed. Activists with strong views about the nature of their disease and what does or does not work in treating it have never accepted the result and have attempted to discredit the conduct of the trial and those who led it. Many academics have also raised concerns about the trial's conduct.

[Link to continuation in full text of Article in the BMJ.]

HEADACHE and MIGRAINE

Predictors of allodynia in persons with migraine: Results from the Migraine in America Symptoms and Treatment (MAST) study.

Dodick DW[1], Reed ML[2], Fanning KM[2], Munjal S[3], Alam A[3], Buse DC[4], Schwedt TJ[1], Lipton RB[4].

Cephalalgia. **2019 Feb 7**:333102418825346. doi: 10.1177/0333102418825346. PMID: 30732460. [Epub ahead of print]

BACKGROUND: Cutaneous allodynia is a common clinical feature of migraine that has been associated with reduced efficacy of acute migraine treatments and an increased risk of disease progression.

OBJECTIVE: Identify factors associated with allodynia in a sample of adults with migraine.

METHODS: An online survey panel was used to identify adults with migraine who averaged at least 1 monthly headache day over the previous 3 months. Data on sociodemographics, headache frequency, headache pain intensity, migraine symptom severity, medication use, depression and anxiety, and cutaneous allodynia (via the Allodynia Symptom Checklist) were obtained. Binary logistic modeling predicted the presence of allodynia. Odds ratios and 95% confidence intervals (CI) were calculated.

RESULTS: In total, 15,133 individuals with migraine met the eligibility criteria. Mean age was 43.1 years, 73.0% were female, and 81.0% were Caucasian. Allodynia was present in 39.9%. The fully adjusted model, controlling for sociodemographics and headache features, demonstrated that allodynia was significantly associated with a higher migraine symptom severity score (odds ratio 1.17, confidence interval 1.15, 1.19) and more severe pain intensity (odds ratio 1.11, confidence interval 1.08, 1.14); probable depression and/or anxiety (odds ratio 1.83, confidence interval 1.67, 2.00); and overuse of acute medication (odds ratio 1.23, confidence interval 1.09, 1.38). A higher number of monthly headache days increased the likelihood of allodynia, but the effect was attenuated in the fully adjusted model.

CONCLUSION: In a representative sample of US adults with migraine, there were significant associations between allodynia and headache frequency and intensity, anxiety and/or depression, symptom severity, and acute medication overuse.

HEADACHE and MIGRAINE (Continued)

Relating Photophobia, Visual Aura, and Visual Triggers of Headache and Migraine.

Hayne DP[1,2], Martin PR[3].

Headache. **2019 Feb 8**. doi: 10.1111/head.13486. PMID: 30737782. [Epub ahead of print]

OBJECTIVE: This study investigated a potential association between visual factors and symptoms related to migraine. It was predicted that photophobia and visual aura would be positively associated with interictal light sensitivity and visual headache triggers (flicker, glare, and eyestrain), and that these 2 visual symptoms would also be associated.

BACKGROUND: Previous studies have found independent neurophysiological associations between several visual factors and symptoms related to headache disorders. Many of these connections appear to be associated with increased cortical hypersensitivity, a phenomenon that might be in part due to repeated avoidance and reduced tolerance to triggers. If true, and if associations between visual factors and symptoms can be established, this may have implications for an exposure-based treatment for migraine symptoms.

METHODS: Four hundred and ninety-one participants (411 female, 80 male) were recruited through Griffith University (AUS), Headache Australia, Pain Australia, and through social media. Participants were grouped based on the presence of headache disorder symptoms and the presence or absence of photophobia and/or visual aura. A cross-sectional online survey design was utilized to gather information pertaining to interictal light sensitivity, visual triggers, and visual symptoms.

RESULTS: With respect to interictal light sensitivity and photophobia, a significant difference ($P < .001$, eta squared [η^2] = 0.084) was found between the 3 groups, where headache disorder participants with photophobia (group A1; mean [M] = 2.5, standard deviation [SD] = 0.97) reported significantly greater light sensitivity than participants with headache disorder and no photophobia (A2; M = 1.68, SD = 0.62) and control group participants (A3; M = 1.82, SD = 0.85). This pattern was repeated for participants reporting flicker as a headache trigger ($P < .001$, $\eta^2 = 0.061$), with group A1 (M = 2.45, SD = 1.24) significantly higher than groups A2 (M = 1.68, SD = 0.83) and A3 (M = 1.68, SD = 0.89), and was also seen for glare as a headache trigger ($P < .001$, $\eta^2 = 0.092$), with group A1 (M = 2.92, SD = 0.96) significantly higher than A2 (M = 2.31, SD = 0.89) and A3 (M = 2.09, SD = 0.93). This pattern of results was not replicated for headache disorder participants with and without visual aura. A significant association ($P < .001$) was found between photophobia and visual aura in headache disorder participants based on a chi-square test of independence, with 86/136 participants reporting either both or neither visual symptom.

CONCLUSIONS: This study supports a link between certain visual phenomena in headache disorder populations, and supports future research into exposure-based treatments for migraine symptoms.

Effect of coenzyme Q10 supplementation on clinical features of migraine: a systematic review and dose-response meta-analysis of randomized controlled trials.

Parohan M[1,2], Sarraf P[3], Javanbakht MH[1], Ranji-Burachaloo S[3], Djalali M[1].

Nutr Neurosci. **2019 Feb 6**:1-8. doi: 10.1080/1028415X.2019.1572940. PMID: 30727862. [Epub ahead of print]

OBJECTIVE: Coenzyme Q10 is an antioxidant and an essential mitochondrial cofactor which has been suggested to improve the clinical features of migraine. Several randomized clinical trials have examined the effects of Coenzyme Q10 on migraine with inconclusive results. The aim of this systematic review and meta-analysis was to evaluate the impact of Coenzyme Q10 supplementation on the frequency, severity, and duration of migraine attacks.

METHODS: A systematic review of the literature was conducted using ISI Web of Science, PubMed, Cochrane library and Scopus to identify eligible studies up to April 2018. Studies included were randomized clinical trials of Coenzyme Q10 supplementation that reported the frequency, severity, or duration of migraine attacks as a primary outcome. A meta-analysis of eligible studies was performed using the fixed effects model or the random effects model to estimate pooled effect size.

RESULTS: Four randomized clinical trials with 221 participants were included. Coenzyme Q10 supplementation significantly reduced the frequency of migraine attacks (weighted mean difference: -1.87 attacks/month, 95% CI: -2.69 to -1.05, $p < 0.001$) without significant heterogeneity among the studies ($I^2 = 36.6\%$, $p = 0.192$). Coenzyme Q10 supplementation had no significant effect on severity (weighted mean difference: -2.35 visual analog scale score, 95% CI: -5.19 to 0.49, $p = 0.105$) and duration of migraine attacks (weighted mean difference: -6.14 h, 95% CI: -13.14 to 0.87, $p = 0.086$) with high heterogeneity.

CONCLUSION: Pooled analyses of available randomized clinical trials suggest that Coenzyme Q10 supplementation may reduce the frequency of migraine attacks per month without affecting the severity or duration of migraine attacks.

HEADACHE and MIGRAINE (Continued)

Efficacy of ADAM Zolmitriptan for the Acute Treatment of Difficult-to-Treat Migraine Headaches.

Tepper SJ[1,2], Dodick DW[3], Schmidt PC[4], Kellerman DJ[4].

Headache. **2019 Jan 30**. doi: 10.1111/head.13482. PMID: 30698272. [Epub ahead of print]

OBJECTIVE: To understand the efficacy of zolmitriptan applied with Adhesive Dermally Applied Microarray (ADAM) in treating types of migraine (those with severe headache pain, the presence of nausea, treatment ≥2 hours after migraine onset, or migraine present upon awakening) that are historically considered to be less responsive to oral medications.

BACKGROUND: ADAM is an investigational system for intracutaneous drug administration. In a pivotal Phase 2b/3 study (ZOTRIP, N = 321 in the modified intention-to-treat population), ADAM zolmitriptan 3.8 mg provided superior pain freedom and freedom from patients' usual most bothersome associated symptom (MBS), compared with placebo at 2 hours post-dose. We undertook a post hoc analysis of data from the ZOTRIP trial to examine these same outcomes in subsets of patients whose migraine characteristics have been associated with poorer outcomes when treated with oral medications.

METHODS: The ZOTRIP trial was a multicenter, randomized, double-blind, placebo-controlled, parallel group Phase 2b/3 study conducted at 36 sites in the United States. Presented here are post hoc subgroup analyses of patients with nausea (n = 110) or severe pain (n = 72) at baseline, those whose treatment was delayed 2 or more hours after onset (n = 75), and those who awoke with migraine (n = 80). The Cochran-Mantel-Haenszel test was used to assess whether patients in the ADAM zolmitriptan 3.8 mg group had superior treatment outcomes compared with placebo.

RESULTS: In patients with nausea, 2-hour pain freedom was achieved in 44% (26/59) in the ADAM zolmitriptan 3.8 mg group and 14% (7/51) in the placebo group (P = .005) (odds ratio = 5.11, 95% CI: 1.96-13.30), and 2-hour MBS freedom was achieved in 68% (40/59) in the active treatment group and 45% (23/51) of those receiving placebo (P = .009) (odds ratio = 2.86, 95% CI: 1.28-6.43). For those with severe pain, corresponding pain-free values were 26% (10/39) and 15% (5/33) (P = .249) (odds ratio = 2.14, 95% CI: 0.60-7.62), and MBS-free values were 64% (25/39) and 42% (14/33) (P = .038) (odds ratio = 2.86, 95% CI: 1.05-7.79). Among participants who awoke with migraine, 44% (16/36) and 16% (7/44) were pain-free in the ADAM zolmitriptan 3.8 mg and placebo groups, respectively (P = .006) (odds ratio = 4.29, 95% CI: 1.50-12.31), and 72% (26/36) vs 39% (17/44) were MBS-free, respectively (P = .003) (odds ratio = 4.40, 95% CI: 1.61-12.05). In those whose treatment was delayed ≥2 hours, pain freedom in the active treatment group and placebo group were 33% (12/36) and 10% (4/39), respectively (P = .017) (odds ratio = 4.33, 95% CI: 1.24-15.10), and MBS freedom was achieved in 69% (25/36) and 41% (16/39), respectively, in the delayed treatment group (P = .014) (odds ratio = 3.37, 95% CI: 1.27-8.95). No significant effects (overall interaction P = .353) were observed in logistical regression models of treatment by subgroup interaction.

CONCLUSION: Severe pain, delayed treatment, awakening with a headache, and the presence of nausea are factors that predict a poorer response to acute migraine treatment. In these post hoc analyses of subgroups of patients with each of these characteristics in the ZOTRIP trial, participants receiving ADAM zolmitriptan 3.8 mg displayed nearly uniformly better headache responses (2-hour headache freedom and 2-hour MBS freedom) compared with those who received placebo.

CHRONIC PAIN

Association Between Predeployment Optimism and Onset of Postdeployment Pain in US Army Soldiers.

Hassett AL[1], Fisher JA[2,3], Vie LL[2,3], Kelley WL[2, 3], Clauw DJ[1], Seligman MEP[2].

JAMA Netw Open. **2019 Feb 1**;2(2):e188076. doi: 10.1001/jamanetworkopen.2018.8076. PMID: 30735237.

Importance: Pain after deployment is a major health care concern. While risk factors have been previously studied, few studies have explored protective factors.

Objective: To examine the prospective association between predeployment optimism and the onset of new pain after deployment in US Army soldiers.

Design, Setting, and Participants: This prospective longitudinal cohort study examined US Army soldiers (active duty, Reserve, and National Guard) who deployed to Afghanistan or Iraq between February 12, 2010, and August 29, 2014, and completed the necessary psychological and health assessments before and after deployment. Analyses were performed in the Person-Event Data Environment between July 2016 and November 2018. This study relied exclusively on existing, secondary Army data. Of the 413 763 Army soldiers who met the specified deployment criteria, 385 925 soldiers were missing 1 or more of the required assessment forms. Of the remaining 27 838 soldiers who were examined for eligibility, 7104 soldiers were excluded because of preexisting back pain, joint pain, or frequent headaches. These exclusions resulted in a final analytic sample of 20 734 eligible soldiers.

Main Outcomes and Measures: This study examined new reports of pain after deployment, including new back pain, joint pain, and frequent headaches.

Results: Among 20 734 US Army soldiers (87.8% male; mean [SD] age, 29.06 [8.42] years), 37.3% reported pain in at least 1 new area of the body after deployment: 25.3% reported new back pain, 23.1% reported new joint pain, and 12.1% reported new frequent headaches. As a continuous measure, each 1-U increase in optimism was associated with 11% lower odds of reporting any new pain after deployment, even while adjusting for demographic, military, and combat factors (odds ratio, 0.89; 95% CI, 0.86-0.93). Tertile analyses revealed that compared with soldiers with high optimism (lowest odds of new pain) soldiers with low optimism had 35% greater odds of reporting new pain in any of the 3 sites evaluated (odds ratio, 1.35; 95% CI, 1.21-1.50). In addition, a larger increase in risk of new pain was observed when comparing the moderate-optimism and low-optimism groups rather than the high-optimism and moderate-optimism groups.

Conclusions and Relevance: Higher levels of optimism were associated with lower odds of reporting new pain after deployment, over and above other common determinants of pain, including demographic and military characteristics and combat experiences. Soldiers with low levels of optimism before deployment could benefit from programs geared toward enhancing optimism.

Posttraumatic Stress Symptoms Mediate the Effects of Trauma Exposure on Clinical Indicators of Central Sensitization in Patients With Chronic Pain.

McKernan LC[1,2], Johnson BN[3], Crofford LJ[4], Lumley MA[5], Bruehl S[6], Cheavens JS[7].

Clin J Pain. **2019 Feb 5**. doi: 10.1097/AJP.0000000000000689. PMID: 30730446. [Epub ahead of print]

OBJECTIVE: Evidence supports high rates of co-occurrence of posttraumatic stress disorder (PTSD) and chronic pain disorders involving central sensitization (CS). The nature of this relationship, however, remains relatively unexplored. In this study, we aimed to (1) assess how both trauma exposure and current PTSD symptoms are related to clinical manifestations of CS, and (2) test whether PTSD symptoms explain the relationship between trauma exposure and CS. Because experiential avoidance has been shown to impact the relationship between trauma and health outcomes, we (3) explored experiential avoidance as a possible mediator or moderator of the trauma-CS relationship.

METHODS: A sample of 202 adult patients (79% female) with chronic pain completed validated self-report measures of trauma exposure, current PTSD symptoms, experiential avoidance, and three manifestations of CS: widespread pain, greater pain severity, and polysomatic symptom reporting. We used path analysis and multivariate regression to assess our study aims.

RESULTS: Both trauma exposure and PTSD symptoms were significantly associated with all three clinical indicators of CS. PTSD symptoms partially explained the relationship between trauma exposure and widespread pain, pain intensity, and polysomatic symptoms. Experiential avoidance did not mediate or moderate the trauma-CS relationship.

CONCLUSION: Our findings suggest that trauma exposure is linked to elevated clinical markers of CS, but a critical factor in this relationship is the mediating effect of current PTSD symptoms.

OTHER RESEARCH OF INTEREST

Blood-brain barrier breakdown is an early biomarker of human cognitive dysfunction.

Nation DA[1,2,3], Sweeney MD[1], Montagne A[1], Sagare AP[1], D'Orazio LM[2,4], Pachicano M[1], Sepehrband F[5], Nelson AR[1], Buennagel DP[6], Harrington MG[6], Benzinger TLS[7,8], Fagan AM[8,9,10], Ringman JM[2,4], Schneider LS[2,4,11], Morris JC[8,9], Chui HC[2,4], Law M[2,5,12], Toga AW[2,5], Zlokovic BV[13,14].

Nat Med. **2019 Jan 14**. doi: 10.1038/s41591-018-0297-y. PMID: 30643288. [Epub ahead of print]

Vascular contributions to cognitive impairment are increasingly recognized as shown by neuropathological, neuroimaging, and cerebrospinal fluid biomarker studies. Moreover, small vessel disease of the brain has been estimated to contribute to approximately 50% of all dementias worldwide, including those caused by Alzheimer's disease (AD). Vascular changes in AD have been typically attributed to the vasoactive and/or vasculotoxic effects of amyloid-β (Aβ), and more recently tau. Animal studies suggest that Aβ and tau lead to blood vessel abnormalities and blood-brain barrier (BBB) breakdown. Although neurovascular dysfunction and BBB breakdown develop early in AD, how they relate to changes in the AD classical biomarkers Aβ and tau, which also develop before dementia, remains unknown. To address this question, we studied brain capillary damage using a novel cerebrospinal fluid biomarker of BBB-associated capillary mural cell pericyte, soluble platelet-derived growth factor receptor-β, and regional BBB permeability using dynamic contrast-enhanced magnetic resonance imaging. Our data show that individuals with early cognitive dysfunction develop brain capillary damage and BBB breakdown in the hippocampus irrespective of Alzheimer's Aβ and/or tau biomarker changes, suggesting that BBB breakdown is an early biomarker of human cognitive dysfunction independent of Aβ and tau.

Integrating Health Care and Social Services for People with Serious Illness: Proceedings of a Workshop.

Editors: Roundtable on Quality Care for People with Serious Illness; Board on Health Care Services; Board on Health Sciences Policy; Health and Medicine Division; National Academies of Sciences, Engineering, and Medicine.

Rapporteurs: Laurene Graig, Sylara Marie Cruz and Joe Alper

Washington (DC): National Academies Press (US); **2019 January.** DOI: 17226/25350. PMID: 30640417.

Prepublication Draft: This title is currently only available in Bookshelf as a prepublication draft version in PDF format (1.6M). The final version is forthcoming.

A growing body of research indicates that social determinants of health, defined by the World Health Organization as “the conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life,” have a significant impact on health care utilization and outcomes. Researchers and policymakers in the United States have spent decades exploring and discussing approaches to integrating health care and social services. While no nation has a truly integrated system, many other industrialized nations invest more heavily in social services than the United States, and are more effective in integrating these services with health care. Such integration is seen both as a way to improve quality of care and health outcomes, as well as to control overall health care costs. Indeed, a number of studies have sought to quantify the health gains associated with a range of social service interventions (Bradley et al., 2016). Integrating health care and social services, such as accessible housing, meals and nutrition services, transportation, and caregiver training, is particularly important for those facing serious illness who typically encounter multiple chronic conditions, pain and other symptoms, functional dependency, frailty, and significant family caregiver needs.

In an effort to better understand and facilitate discussions about the challenges and opportunities related to integrating health care and social services for people with serious illness, the Roundtable on Quality Care for People with Serious Illness of the National Academies of Sciences, Engineering, and Medicine (The National Academies) held a full-day public workshop on July 19, 2018 in Washington, DC. The workshop, *Integrating Health Care and Social Services for People with Serious Illness*, featured a broad range of experts and stakeholders including researchers, policy analysts, patient and family caregiving advocates, and representatives of federal agencies. To highlight the critical role of family caregivers in caring for people with serious illness, the workshop featured a session devoted to the unique roles and needs of caregivers, who often serve as a bridge between the health care and social services sectors.

The Roundtable on Quality Care for People with Serious Illness serves to convene stakeholders from government, academia, industry, professional associations, nonprofit advocacy groups, and philanthropies. Inspired by and expanding on the work of the Institute of Medicine’s (IOM’s) *Dying in America* report (IOM, 2015), the roundtable aims to foster ongoing dialogue about crucial policy and research issues to accelerate and sustain progress in care for people of all ages experiencing serious illness.

OTHER RESEARCH OF INTEREST (Continued)

ALS-implicated protein TDP-43 sustains levels of STMN2, a mediator of motor neuron growth and repair.

Klim JR[1,2,3,4], Williams LA[1,2,3,4,5], Limone F[1,2,3,4,6], Guerra San Juan I[1,2,3,4,7], Davis-Dusenbery BN[1,2,3,4,8], Mordes DA[1,2,3,4,9], Burberry A[1,2,3,4], Steinbaugh MJ[10], Gamage KK[1,2,3,4,11], Kirchner R[10], Moccia R[1,2,3,4,12], Cassel SH[1,2,3,4,13,14], Chen K[15], Wainger BJ[15,16], Woolf CJ[15], Eggan K[17,18,19,20].

Nat Neurosci. **2019 Feb**;22(2):167-179. doi: 10.1038/s41593-018-0300-4. Epub 2019 Jan 14. PMID: 30643292.

The findings that amyotrophic lateral sclerosis (ALS) patients almost universally display pathological mislocalization of the RNA-binding protein TDP-43 and that mutations in its gene cause familial ALS have nominated altered RNA metabolism as a disease mechanism. However, the RNAs regulated by TDP-43 in motor neurons and their connection to neuropathy remain to be identified. Here we report transcripts whose abundances in human motor neurons are sensitive to TDP-43 depletion. Notably, expression of STMN2, which encodes a microtubule regulator, declined after TDP-43 knockdown and TDP-43 mislocalization as well as in patient-specific motor neurons and postmortem patient spinal cord. STMN2 loss upon reduced TDP-43 function was due to altered splicing, which is functionally important, as we show STMN2 is necessary for normal axonal outgrowth and regeneration. Notably, post-translational stabilization of STMN2 rescued neurite outgrowth and axon regeneration deficits induced by TDP-43 depletion. We propose that restoring STMN2 expression warrants examination as a therapeutic strategy for ALS.

Comparative evaluation of group-based mindfulness-based stress reduction and cognitive behavioural therapy for the treatment and management of chronic pain: A systematic review and network meta-analysis.

Khoo EL[1,2], Small R[1,3], Cheng W[1], Hatchard T[4], Glynn B[1], Rice DB[1,5], Skidmore B[6], Kenny S[1,7], Hutton B[1], Poulin PA[1,8,9].

Evid Based Ment Health. **2019 Feb**;22(1):26-35. doi: 10.1136/ebmental-2018-300062. PMID: 30705039.

QUESTION: This review compares mindfulness-based stress reduction (MBSR) to cognitive-behavioural therapy (CBT) in its ability to improve physical functioning and reduce pain intensity and distress in patients with chronic pain (CP), when evaluated against control conditions.

STUDY SELECTION AND ANALYSIS: Ovid MEDLINE, EmbaseClassic+Embase, PsycINFO and the Cochrane Library were searched to identify randomised controlled trials. The primary outcome measure was physical functioning. Secondary outcomes were pain intensity and depression symptoms. We used random and fixed effects (RE and FE) network meta-analyses (NMA) to compare MBSR, CBT and control interventions on the standardised mean difference scale.

FINDINGS: Twenty-one studies were included: 13 CBT vs control (n=1095), 7 MBSR vs control (n=545) and 1 MBSR vs CBT vs control (n=341). Of the 21 articles, 12 were determined to be of fair or good quality. Findings from RE NMA for change in physical functioning, pain intensity and depression revealed clinically important advantages relative to control for MBSR and CBT, but no evidence of an important difference between MBSR and CBT was found.

CONCLUSIONS: This review suggests that MBSR offers another potentially helpful intervention for CP management. Additional research using consistent measures is required to guide decisions about providing CBT or MBSR.

Cerebellar modulation of the reward circuitry and social behavior.

Carta I[1], Chen CH[1], Schott AL[1], Dorizan S[1], Khodakhah K[2,3,4].

Science. **2019 Jan 18**;363(6424). pii: eaav0581. doi: 10.1126/science.aav0581. PMID: 30655412.

The cerebellum has been implicated in a number of nonmotor mental disorders such as autism spectrum disorder, schizophrenia, and addiction. However, its contribution to these disorders is not well understood. In mice, we found that the cerebellum sends direct excitatory projections to the ventral tegmental area (VTA), one of the brain regions that processes and encodes reward. Optogenetic activation of the cerebello-VTA projections was rewarding and, in a three-chamber social task, these projections were more active when the animal explored the social chamber. Intriguingly, activity in the cerebello-VTA pathway was required for the mice to show social preference in this task. Our data delineate a major, previously unappreciated role for the cerebellum in controlling the reward circuitry and social behavior.

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