GULF WAR ILLNESS

A Two-Hit Model of The Biological Origin of Posttraumatic Stress Disorder (PTSD).

Georgopoulos AP[1,2,3,4,5], James LM[1,2,3,4], Christova P[1,2,3], Engdahl BE[1,2,3,6].

J Ment Health Clin Psychol. **2018 Oct 1**;2(5):9-14. PMID: 30957105.

[Note: Delayed posting in PubMed—Not previously listed in RAC Research Alerts.]

Posttraumatic stress disorder (PTSD) is a debilitating disorder that can develop following exposure to a traumatic event. Although the cause of PTSD is known, the brain mechanisms of its development remain unknown, especially why it arises in some people but not in others. Most of the research on PTSD has dealt with psychological and brain mechanisms underlying its symptomatology, including intrusive memories, fear and avoidance (see ref.1 for a broad coverage of PTSD research)[1]. Here we focus, instead, on the origin of PTSD, namely on the neural mechanisms underlying its development. Specifically, we propose a two-hit model for PTSD development, with the following components. (a) The 1st hit is a neuroimmune challenge, as a preexisting condition, and the 2nd hit is intense glutamatergic neurotransmission, induced by the traumatic event; (b) the key molecule that mediates the effects of these two hits is intercellular adhesion molecule 5 (ICAM-5) which was found to be differentially expressed in PTSD[2]. ICAM-5 is activated by neuroimmune challenge[3,4] and glutamatergic neurotransmission[5,6], it further enhances glutamatergic transmission[6], and exerts a potent effect on synapse formation and neural plasticity, in addition to immunoregulatory functions[3,4,7]; and (c) with respect to the neural network(s) involved, the brain areas most involved are medial temporal cortical areas, and interconnected cortical and subcortical areas[8-10]. We hypothesize that the net result of intense glutamatergic transmission in those areas induced by a traumatic event in the presence of ongoing neuroimmune challenge leads to increased levels of ICAM-5 which further enhances glutamatergic transmission and thus leads to a state of a neural network with highly correlated neural interactions, as has been observed in functional neuroimaging studies[8-10]. We assume that such a "locked-in" network underlies the intrusive re-experiencing in PTSD and maintains associated symptomatology, such as fear and avoidance.

Excerpt from the published article for this abstract in *Journal of Mental Health & Clinical Psychology*:

> Background Immune Challenge: Persistent Antigens and PTSD
>
> Our two-hit model for PTSD development predicts that exposure to trauma in the presence of neuroimmune challenge would increase their risk of developing PTSD. As mentioned above, the presence of inflammation, as indicated by increased plasma CRP, is a risk factor for developing PTSD following trauma exposure[34] and, conversely, the presence of PTSD is a risk factor for subsequently developing an autoimmune disease[43,44]. Moreover, we found in a recent study[45] that Gulf War Illness (GWI), an immune-related disorder[46–48], primes the occurrence of PTSD.
>
> The various mechanisms underlying the interplay between PTSD and associated immune-related comorbidities, and the relevant neuroendocrine alterations involved, have been discussed succinctly[49]. In general, it is not clear which is the primary cause. It is very possible that PTSD and immune-related disorders share common functional alterations, predisposing for each other, that will need further research to be disentangled. Based on our initial findings of reduced Human Leukocyte Antigen (HLA) class 2 protection in GWI[46], and on our more recent finding that HLA allele DRB1*13:02 prevents brain atrophy in GWI[48], we proposed[48] that an important underlying factor for GWI consists of “persistent antigens”, that is, antigens (of various kinds) to which veterans of the 1991 Gulf War were exposed (most probably through the vaccines received) but which could not be eliminated due the lack of HLA protection[46].

See abstract below for the recent study reference number 45 noted in this excerpt.

GULF WAR ILLNESS (Continued)

Brain Function in Gulf War Illness (GWI) and Associated Mental Health Comorbidities.

Engdahl BE[1,2,3,4], James LM[1,2,4,5], Miller RD[1], Leuthold AC[1,2], Lewis SM[1,6], Carpenter AF[1,6], Georgopoulos AP[1,2,4,5,6].

J Neurol Neuromedicine. **2018**;3(4):24-34. PMCID: PMC6417922. PMID: 30882065. **Epub 2018 Jul 19**.

[Note: Delayed posting in PubMed—Not previously listed in RAC Research Alerts.]

GWI has affected a substantial number of Gulf War (GW) veterans. The disease involves several organ systems among which the brain is most prominent. Neurological, cognitive and mood-related (NCM) symptoms frequently dominate and are at the root of chronic ill-health and disability in veterans suffering from GWI. In addition, such symptoms frequently co-occur with diagnosable mental health disorders, predominantly posttraumatic stress disorder (PTSD). Here we investigated the possibility that increased GWI severity leads, above a threshold, to a diagnosable mental health disorder (excluding psychosis). For this purpose, we used, in separate analyses, symptom severity scores and resting-state brain functional connectivity patterns, as determined by magnetoencephalography (MEG). Two-hundred-thirty GW-era veterans participated in this study. They completed diagnostic interviews to establish the presence of GWI and assess mental health status. This distinguished 3 groups: healthy controls (N = 41), veterans with GWI and no mental illness (GWI group, N = 91), and veterans with both GWI and mental health disorder (GWI+MH, N = 98). For each veteran, symptom severity scores in the 6 GWI domains (fatigue, pain, NCM, skin, gastrointestinal, respiratory) were available as well as 9 summary measures of the distribution of Synchronous Neural Interactions (SNI) derived from the MEG recordings. We tested the hypothesis that, in the presence of GWI, the appearance of a diagnosable mental health disorder may depend on GWI symptom severity. For that purpose, we performed a logistic regression on the GWI population, where the presence (or absence) of the MH disorder was the dependent variable and the age- and gender-adjusted GWI severity in the 6-symptom domains were the predictors. The outcome was the probability that a participant will have MH disorder or not. Similarly, we tested the hypothesis that the presence of the MH disorder can be predicted by the SNI distribution patterns by performing a second logistic regression as above but with the 9 SNI measures as predictors. We found GWI symptom severity differed significantly across groups (GWI+MH > GWI > Control). SNI distributions of the GWI group also differed significantly from the other groups in a systematic hemispheric pattern, such that the presence of GWI involved predominantly the left hemisphere, and presence of mental health disorders involved, in addition, the right hemisphere. Both logistic regressions yielded highly significant outcomes, demonstrating that both GWI symptom severity and SNI distribution measures can predict the presence of MH disorder in GWI. Remarkably, the prediction probabilities for MH presence derived from the symptom-based and SNI-based logistic regressions were positively and highly statistically significantly correlated. Taken together, both objective (neural) and subjective (symptoms) indices suggest that GWI is distinct from healthy controls and varies in severity in a continuum that leads, at the higher end, to a diagnosable MH disorder. The positive correlation between the GWI symptom-based and brain-based predicted classifications provides a key link between GWI symptom severity and synchronous neural interactions in the context of mental illness.

CHRONIC FATIGUE SYNDROME

No Updates this Week for Chronic Fatigue Syndrome.

HEADACHE and MIGRAINE

Risk of ischaemic stroke in patients with migraine: a longitudinal follow-up study using a national sample cohort in South Korea.

Lee SY[1], Lim JS[2], Oh DJ[3], Kong IG, Choi HG[4].

BMJ Open. **2019 Apr 2**;9(4):e027701. doi: 10.1136/bmjopen-2018-027701. PMID: 30944141.

OBJECTIVE: Accumulating evidence has supported the association between migraine and stroke, but the causative association remains unclear. We aimed to investigate the risks of different types of stroke in patients with migraine.

DESIGN: A longitudinal follow-up study.

SETTING: Data collected from a national cohort between 2002 and 2013 by the South Korea Health Insurance Review and Assessment.

PARTICIPANTS: We extracted the data from patients with migraine (n=41 585) and 1:4 matched controls (n=1 66 340) and analysed the occurrence of ischaemic and haemorrhagic strokes. The migraine group included participants treated for migraine (International Classification of Disease-10 (ICD-10): G43)≥2 times. Haemorrhagic stroke (I60-I62) and ischaemic stroke (I63) were determined based on the admission histories. The crude and adjusted HRs were calculated using Cox proportional hazard models, and the 95% CI were determined. Subgroup analyses stratified by age and sex were also performed.

RESULTS: Higher rates of ischaemic stroke were observed in the migraine group (2.3% [964/41,585]) than in the control group (2.0% [3294/166 340], P<0.001). The adjusted HR for ischaemic stroke was 1.18 (95% CI=1.10 to 1.26) in the migraine group (P<0.001). Compared with control subjects, participants who reported migraine with aura and migraine without aura had increased adjusted HRs of 1.44 (95% CI=1.09 to 1.89) and 1.15 (95% CI=1.06 to 1.24), respectively, for ischaemic stroke, but no increased risk of haemorrhagic stroke. In our subgroup analysis, a strong association between migraine and ischaemic stroke was observed in young patients, specifically young women. The contribution of migraine to the occurrence of ischaemic stroke was also observed in middle-aged women and old women (each P<0.05). The risk of haemorrhagic stroke did not reach statistical significance in any age group.

CONCLUSION: Migraine is associated with an increased risk of ischaemic stroke, but not haemorrhagic stroke.

Suicide Attempts among Those with Migraine: Findings from a Nationally Representative Canadian Study.

Fuller-Thomson E, Hodgins GA.

Arch Suicide Res. **2019 Apr 4**:1-20. doi: 10.1080/13811118.2019.1578710. PMID: 30945611 [Epub ahead of print]

The objectives of this study were to identify the gender-specific prevalence of suicide attempts among those with migraine and to examine what factors are associated with suicide attempts among migraineurs. This study was a nationally representative analysis of the 2012 Canadian Community Health Survey - Mental Health (CCHS-MH) with 21,744 respondents, of whom 2,223 had migraine. Bivariate and logistic regression analyses were conducted. Those with migraine had a much higher prevalence of ever attempting suicide than those without migraine (men: 7.5% vs 1.9%; women; 9.3% vs 2.7%, p < .001). Among migraineurs, the odds of suicide attempts were higher among poorer respondents, those in chronic pain and those with a history of childhood adversities, substance dependence and/or mental illness. Targeted outreach is needed to reduce suicidality in this vulnerable population.

HEADACHE and MIGRAINE (Continued)

Large-scale plasma metabolome analysis reveals alterations in HDL metabolism in migraine.

Onderwater GLJ[1], Ligthart L[1], Bot M[1], Demirkan A[1], Fu J[1], van der Kallen CJH[1], Vijfhuizen LS[1], Pool R[1], Liu J[1], Vanmolkot FHM[1], Beekman M[1], Wen KX[1], Amin N[1], Thesing CS[1], Pijpers JA[1], Kies DA[1], Zielman R[1], de Boer I[1], van Greevenbroek MMJ[1], Arts ICW[1], Milaneschi Y[1], Schram MT[1], Dagnelie PC[1], Franke L[1], Ikram MA[1], Ferrari MD[1], Goeman JJ[1], Slagboom PE[1], Wijmenga C[1], Stehouwer CDA[1], Boomsma DI[1], van Duijn CM[1], Penninx BW[1], 't Hoen PAC[1], Terwindt GM[1], van den Maagdenberg AMJM[2]; BBMRI Metabolomics Consortium.

Neurology. **2019 Apr 3**. pii: 10.1212/WNL.0000000000007313. doi: 10.1212/WNL.0000000000007313. PMID: 30944236. [Epub ahead of print]

OBJECTIVE: To identify a plasma metabolomic biomarker signature for migraine.

METHODS: Plasma samples from 8 Dutch cohorts (n = 10,153: 2,800 migraine patients and 7,353 controls) were profiled on a ^{1}H-NMR-based metabolomics platform, to quantify 146 individual metabolites (e.g., lipids, fatty acids, and lipoproteins) and 79 metabolite ratios. Metabolite measures associated with migraine were obtained after single-metabolite logistic regression combined with a random-effects meta-analysis performed in a nonstratified and sex-stratified manner. Next, a global test analysis was performed to identify sets of related metabolites associated with migraine. The Holm procedure was applied to control the family-wise error rate at 5% in single-metabolite and global test analyses.

RESULTS: Decreases in the level of apolipoprotein A1 (β -0.10; 95% confidence interval [CI] -0.16, -0.05; adjusted p = 0.029) and free cholesterol to total lipid ratio present in small high-density lipoprotein subspecies (HDL) (β -0.10; 95% CI -0.15, -0.05; adjusted p = 0.029) were associated with migraine status. In addition, only in male participants, a decreased level of omega-3 fatty acids (β -0.24; 95% CI -0.36, -0.12; adjusted p = 0.033) was associated with migraine. Global test analysis further supported that HDL traits (but not other lipoproteins) were associated with migraine status.

CONCLUSIONS: Metabolic profiling of plasma yielded alterations in HDL metabolism in migraine patients and decreased omega-3 fatty acids only in male migraineurs.

Increased risk of sleep apnoea among primary headache disorders: a nationwide population-based longitudinal study.

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

Postgrad Med J. **2019 Apr 1**. pii: postgradmedj-2018-136220. doi: 10.1136/postgradmedj-2018-136220. PMID: 30936249. [Epub ahead of print]

BACKGROUND: Primary headache disorders (PHDs) are associated with sleep problems. It is suggested that headache and sleep disorder share anatomical and physiological characteristics. We hypothesised that patients with PHDs were exposed to a great risk for developing sleep apnoea (SA).

METHODS: In this retrospective longitudinal study, the data obtained from the Longitudinal Health Insurance Database in Taiwan were analysed. The study included 1346 patients with PHDs who were initially diagnosed and 5348 patients who were randomly selected and age/sex matched with the study group as controls. PHDs, SA, comorbidities and other confounding factors were defined based on International Classification of Diseases, Ninth Revision, Clinical Modification. Cox proportional hazards regressions were employed to examine adjusted HRs after adjusting with confounding factors.

RESULTS: Our data revealed that patients with PHDs had a higher risk (HR 2.17, 95% CI 1.259 to 3.739, p<0.05) to develop SA compared with matched cohorts, whereas patients with migraine exhibited a high risk (HR 2.553, 95% CI 1.460 to 4.395, p<0.01). The results showed that patients with PHDs aged 18-44 exhibited highest risk of developing SA. In addition, males with PHDs exhibited an HR 3.159 (95% CI 1.479 to 6.749, p<0.01) for developing SA, respectively. The impact of PHDs on SA risk was progressively increased by various follow-up time intervals.

CONCLUSION: Our results suggest that PHDs are linked to an increased risk for SA with sex-dependent and time-dependent characteristics.

CHRONIC PAIN

Suicide Attempts among Those with Migraine: Findings from a Nationally Representative Canadian Study.

Fuller-Thomson E, Hodgins GA.

Arch Suicide Res. **2019 Apr 4**:1-20. doi: 10.1080/13811118.2019.1578710. PMID: 30945611. [Epub ahead of print]

The objectives of this study were to identify the gender-specific prevalence of suicide attempts among those with migraine and to examine what factors are associated with suicide attempts among migraineurs. This study was a nationally representative analysis of the 2012 Canadian Community Health Survey - Mental Health (CCHS-MH) with 21,744 respondents, of whom 2,223 had migraine. Bivariate and logistic regression analyses were conducted. Those with migraine had a much higher prevalence of ever attempting suicide than those without migraine (men: 7.5% vs 1.9%; women; 9.3% vs 2.7%, $p < .001$). Among migraineurs, the odds of suicide attempts were higher among poorer respondents, those in chronic pain and those with a history of childhood adversities, substance dependence and/or mental illness. Targeted outreach is needed to reduce suicidality in this vulnerable population.

Health Literacy, Opioid Misuse, and Pain Experience Among Adults with Chronic Pain.

Rogers AH[1], Bakhshaie J[1], Orr MF[2], Ditre JW[3], Zvolensky MJ[1,4,5].

Pain Med. **2019 Apr 2**. pii: pnz062. doi: 10.1093/pm/pnz062. PMID: 30938818. [Epub ahead of print]

BACKGROUND: Chronic pain is a significant public health problem that is associated with several negative health outcomes, including increased health care cost, decreased productivity, and prescription opioid misuse. Although efforts have been made to curb the growing opioid epidemic in the United States, further research is needed to better understand individual difference factors that may be associated with greater pain and opioid misuse. Lower levels of health literacy, defined as the ability to obtain, understand, and use health information to make important decisions regarding health and medical care, has been associated with several chronic illnesses. Yet little work has examined the relationship between health literacy, pain, and opioid misuse among individuals with chronic pain.

METHODS: The current study examined health literacy in relation to current opioid misuse, severity of opioid dependence, pain severity, and pain disability among 445 adults with chronic pain (74.6% female, Mage [SD] = 38.45 [11.06] years).

RESULTS: Results indicated that health literacy was significantly negatively associated with each of the criterion variables.

CONCLUSIONS: These results suggest that health literacy may contribute to opioid misuse and pain experience among individuals with chronic pain. Interventions targeting health literacy among individuals with chronic illness may help to address the opioid public health crisis.

Measuring stigma in chronic pain: Preliminary investigation of instrument psychometrics, correlates, and magnitude of change in a prospective cohort attending interdisciplinary treatment.

Scott W[1], Yu L[2], Patel S[2], McCracken LM[3].

J Pain. **2019 Mar 30**. pii: S1526-5900(19)30700-X. doi: 10.1016/j.jpain.2019.03.011. PMID: 30940501. [Epub ahead of print]

Chronic pain is a potentially stigmatizing condition. However, stigma has received limited empirical investigation in people with chronic pain. Therefore, we examined the psychometric properties of a self-report questionnaire of stigma in people with chronic pain attending interdisciplinary treatment. Secondarily, we undertook an exploratory examination of the magnitude of change in stigma associated with interdisciplinary treatment in a prospective observational cohort. Participants attending interdisciplinary treatment based on Acceptance and Commitment Therapy completed the Stigma Scale for Chronic Illness eight-item version (SSCI-8; previously developed and validated in neurological samples), and measures of perceived injustice, pain acceptance, and standard pain outcomes before (n=300) and after treatment (n=247). A unidimensional factor structure and good internal consistency were found for the SSCI-8. Total SSCI-8 scores were correlated with pain intensity, indices of functioning, and depression in bivariate analyses. Stigma scores were uniquely associated with functioning and depression in multiple regression analyses controlling for demographic factors, pain intensity, pain acceptance, and perceived injustice at baseline. SSCI-8 total scores did not significantly improve following treatment, although an exploratory subscale analysis showed a small improvement on internalized stigma. In contrast, scores on perceived injustice, pain acceptance, and pain outcomes improved significantly. Taken together, these data support the reliability and validity of the SSCI-8 for use in samples with chronic pain. Further research is needed optimise interventions to target stigma at both the individual and societal levels. Perspective: This study supports the use of the SSCI-8 to measure stigma in chronic pain. Stigma is uniquely associated with worse depression and pain-related disability. Research is needed to identify how to best target pain-related stigma from individual and societal perspectives.

CHRONIC PAIN (Continued)

DRG FOCUS: A Multicenter Study Evaluating Dorsal Root Ganglion Stimulation and Predictors for Trial Success.

Hunter CW[1], Sayed D[2], Lubenow T[3], Davis T[4], Carlson J[5], Rowe J[6], Justiz R[7], McJunkin T[5], Deer T[8], Mehta P[9], Falowski S[10], Kapural L[11], Pope J[12], Mekhail N[13].

Neuromodulation. **2019 Jan**;22(1):61-79. doi: 10.1111/ner.12796. PMID: 30085382. **Epub 2018 Aug 7**.

[Note: Delayed posting in PubMed—Not previously listed in RAC Research Alerts.]

INTRODUCTION: Dorsal root ganglion stimulation (DRGS) is a powerful tool in the treatment of chronic, neuropathic pain. The premise of DRGS is similar to that of conventional spinal cord stimulation (cSCS), however, there is more variability in how it can be utilized. While it is this variability that likely gives it its versatility, DRGS is not as straightforward to implement as cSCS. The purpose of this study was to assess the efficacy of DRGS on a broad number of diagnoses, determine which dorsal root ganglia were associated with better outcomes for particular body parts/diagnoses, and evaluate what factors/parameters were associated with higher rates of trial success.

METHODS: This is a physician initiated, multicenter retrospective registry of 217 patients trialed with DRGS. Data were collected via an online questionnaire that assessed specifics regarding the patient's pain, distribution, size, and response to treatment. The data were analyzed to see if there were certain diagnoses and/or parameters that were more or less associated with trial success.

RESULTS: DRGS was found to be an effective treatment in all diagnoses evaluated within this study, most of which had statistically significant improvements in pain. The most important predictor of trial success was the amount of painful area covered by paresthesias during the programing phase. The number of leads utilized had a direct and indirect impact on trial success. Pain in the distribution of a specific peripheral nerve responded best and there was no statistical difference based on what body part was being treated.

CONCLUSION: DRGS can be an effective treatment for a variety of neuropathic pain syndromes, in addition to CRPS. It is recommended that a minimum of 2 leads should be utilized per area being treated. In addition, this therapy was shown to be equally efficacious in any body part/region so long as the area being treated is focal and not widespread.

The Mediating Effect of Pain Catastrophizing on PTSD Symptoms and Pain Outcome.

Gilliam WP[1], Craner JR[2,3], Schumann ME[1], Gascho K[1].

Clin J Pain. **2019 Apr 3**. doi: 10.1097/AJP.0000000000000713. PMID: 30950871. PMID: 30953765. [Epub ahead of print]

OBJECTIVE: Co-prevalence of chronic pain and post-traumatic stress disorder (PTSD) negatively impacts the course of both disorders. Patients diagnosed with both conditions report greater pain, affective distress and disability when compared to those with either chronic pain or PTSD alone. While the prevalence and complexity of the comorbidity is widely acknowledged, there is a dearth of research examining potential mechanism variables that might account for the relationship between chronic pain and PTSD. The current study utilizes a series of mediation analyses to examine if pain catastrophizing mediates the relationship between PTSD symptomatology and chronic pain outcome.

METHODS: 203 treatment seeking participants admitted to a three-week interdisciplinary pain rehabilitation program completed a battery of psychometrically validated measures of pain severity, pain interference, pain catastrophizing, depressive symptoms and PTSD symptoms at program admission.

RESULTS: A series of multiple parallel mediation analyses revealed that pain catastrophizing fully mediated the relationships between PTSD symptoms and pain outcome (i.e., pain severity and pain interference) above and beyond the influence of depressive symptoms.

DISCUSSION: Results suggest that pain catastrophizing may represent an important cognitive mechanism through which PTSD symptoms influence the experience of chronic pain. Psychosocial treatment approaches that directly target tendency to catastrophize in response to pain may hold the potential to have salutary effects on both chronic pain and PTSD.

CHRONIC PAIN (Continued)

Altered gut microbiota and endocannabinoid system tone in vitamin D deficiency-mediated chronic pain.

Guida F[1], Boccella S[2], Belardo C[2], Iannotta M[2], Piscitelli F[3], De Filippis F[4], Paino S[2], Ricciardi F[2], Siniscalco D[2], Marabese I[2], Luongo L[2], Ercolini D[4], Di Marzo V[5], Maione S[6].

Brain Behav Immun. **2019 Apr 3**. pii: S0889-1591(18)31247-9. doi: 10.1016/j.bbi.2019.04.006. [Epub ahead of print]

Recent evidence points to the gut microbiota as a regulator of brain and behavior, although it remains to be determined if gut bacteria play a role in chronic pain. The endocannabinoid system is implicated in inflammation and chronic pain processing at both the gut and central nervous system (CNS) levels. In the present study, we used low Vitamin D dietary intake in mice and evaluated possible changes in gut microbiota, pain processing and endocannabinoid system signaling. Vitamin D deficiency induced a lower microbial diversity characterized by an increase in Firmicutes and a decrease in Verrucomicrobia and Bacteroidetes. Concurrently, vitamin D deficient mice showed tactile allodynia associated with neuronal hyperexcitability and alterations of endocannabinoid system members (endogenous mediators and their receptors) at the spinal cord level. Changes in endocannabinoid (anandamide and 2-arachidonoylglycerol) levels were also observed in the duodenum and colon. Remarkably, the anti-inflammatory anandamide congener, palmitoylethanolamide, counteracted both the pain behaviour and spinal biochemical changes in vitamin D deficient mice, whilst increasing the levels of Akkermansia, Eubacterium and Enterobacteriaceae, as compared with vehicle-treated mice. Finally, induction of spared nerve injury in normal or vitamin D deficient mice was not accompanied by changes in gut microbiota composition. Our data suggest the existence of a link between Vitamin D deficiency - with related changes in gut bacterial composition - and altered nociception, possibly via molecular mechanisms involving the endocannabinoid and related mediator signaling systems.

IRRITABLE BOWEL SYNDROME

Food-related quality of life in patients with inflammatory bowel disease and irritable bowel syndrome.

Guadagnoli L[1], Mutlu EA[2], Doerfler B[1], Ibrahim A[2], Brenner D[1], Taft TH[3].

Qual Life Res. **2019 Mar 21**. doi: 10.1007/s11136-019-02170-4. PMID: 30900206. [Epub ahead of print]

BACKGROUND: Food-related quality of life (FRQoL) evaluates the impact of diet, eating behaviors, and food-related anxiety on a person's quality of life. This is the first study to evaluate FRQoL in inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS), two illnesses where food and diet are of importance.

METHODS: One hundred seventy-five participants (80 IBS, 95 IBD) participated in the study by completing measures evaluating FRQoL, psychological distress, and health-related quality of life. Primary analyses evaluated differences in FRQoL between IBD and IBS patients. Secondary analyses compared differences based on remission status, dietary use, and dietary consultation, as well as evaluated potential predictors of FRQoL.

RESULTS: IBD patients in remission report the highest FRQoL (IBD-remission: 91.2 (26.5) vs. IBD-active: 67.7 (19.6) and IBS-active: 67.6 (18.3), $p < .001$). Using more dietary treatments is associated with decreased FRQoL for IBS ($r = -0.23$, $p < .05$) and IBD patients ($r = -0.31$, $p < .01$). IBS patients are more likely to use dietary treatments than IBD (IBS = 81% vs. IBD = 64%, $p < .01$), with self-directed diets being the most commonly used approach. Symptom severity is the strongest predictor of FRQoL in both groups (IBD: $R^2 = .27$, $p < .01$; IBS: $R^2 = .23$, $p < .001$).

CONCLUSION: FRQoL is a unique construct for IBD and IBS patients that can be influenced by several clinical and dietary factors, including number of diets and type of diet used, depending on the diagnosis. Thus, FRQoL should be considered when working with both IBD and IBS patients.

IRRITABLE BOWEL SYNDROME (Continued)

Evidence for an association of gut microbial Clostridia with brain functional connectivity and gastrointestinal sensorimotor function in patients with irritable bowel syndrome, based on tripartite network analysis.

Labus JS[1], Osadchiy V[1], Hsiao EY[1,2], Tap J[3], Derrien M[3], Gupta A[1], Tillisch K[1], Le Nevé B[3], Grinsvall C[4], Ljungberg M[5], Öhman L[4,6], Törnblom H[4], Simren M[4,7], Mayer EA[8].

Microbiome. **2019 Mar 21**;7(1):45. doi: 10.1186/s40168-019-0656-z. PMID: 30898151.

BACKGROUND AND AIMS: Evidence from preclinical and clinical studies suggests that interactions among the brain, gut, and microbiota may affect the pathophysiology of irritable bowel syndrome (IBS). As disruptions in central and peripheral serotonergic signaling pathways have been found in patients with IBS, we explored the hypothesis that the abundance of serotonin-modulating microbes of the order Clostridiales is associated with functional connectivity of somatosensory brain regions and gastrointestinal (GI) sensorimotor function.

METHODS: We performed a prospective study of 65 patients with IBS and 21 healthy individuals (controls) recruited from 2011 through 2013 at a secondary/tertiary care outpatient clinic in Sweden. Study participants underwent functional brain imaging, rectal balloon distension, a nutrient and lactulose challenge test, and assessment of oroanal transit time within a month. They also submitted stool samples, which were analyzed by 16S ribosomal RNA gene sequencing. A tripartite network analysis based on graph theory was used to investigate the interactions among bacteria in the order Clostridiales, connectivity of brain regions in the somatosensory network, and GI sensorimotor function.

RESULTS: We found associations between GI sensorimotor function and gut microbes in stool samples from controls, but not in samples from IBS patients. The largest differences between controls and patients with IBS were observed in the Lachnospiraceae incertae sedis, Clostridium XIVa, and Coprococcus subnetworks. We found connectivity of subcortical (thalamus, caudate, and putamen) and cortical (primary and secondary somatosensory cortices) regions to be involved in mediating interactions among these networks.

CONCLUSIONS: In a comparison of patients with IBS and controls, we observed disruptions in the interactions between the brain, gut, and gut microbial metabolites in patients with IBS-these involve mainly subcortical but also cortical regions of brain. These disruptions may contribute to altered perception of pain in patients with IBS and may be mediated by microbial modulation of the gut serotonergic system.

OTHER RESEARCH OF INTEREST

Evaluation of the Disability Determination Process for Traumatic Brain Injury in Veterans.

Committee on the Review of the Department of Veterans Affairs Examinations for Traumatic Brain Injury; Board on Health Care Services; Health and Medicine Division; A Consensus Study Report of The National Academies of Sciences, Engineering, and Medicine.

Committee Chair: Dan Blazer, II. Study Director: Carolyn Fulco.

Washington (DC): National Academies Press (US); **April 10, 2019.** doi: https://doi.org/10.17226/25317.

Report Highlights: (HTML). Publication Online: (PDF format).

At the mandate of the U.S. Congress, the Department of Veterans Affairs (VA) contracted with the National Academies of Sciences, Engineering, and Medicine to convene a committee to review the process by which the VA assesses impairments relating to TBI for purposes of awarding disability compensation.

In the resulting report, Evaluation of the Disability Determination Process for Traumatic Brain Injury in Veterans, the committee outlines its findings and provides recommendations to the VA related to the health care specialists who diagnose TBI; the adequacy of the tools used by VA to provide clinical examinations and disability ratings for TBI; and the adjudication process (the overall process used to evaluate for disability compensation, from submission of claims through appeals).

OTHER RESEARCH OF INTEREST (Continued)

Using fMRI connectivity to define a treatment-resistant form of post-traumatic stress disorder.

Etkin A[1,2,3,4], Maron-Katz A[5,2,3,4], Wu W[5,2,3,4,6], Fonzo GA[5,2,3,4], Huemer J[5,2,3], Vértes PE[7,8,9], Patenaude B[5,2,3,4], Richiardi J[10,11], Goodkind MS[12,13], Keller CJ[5,2,3,4], Ramos-Cejudo J[4,14], Zaiko YV[5,2,3], Peng KK[5,3], Shpigel E[5,2,3,4], Longwell P[5,2,3,4], Toll RT[5,2,3,4], Thompson A[5], Zack S[5], Gonzalez B[4,14], Edelstein R[5,2,3,4], Chen J[4,14], Akingbade I[5,3,4], Weiss E[5,3], Hart R[4,14], Mann S[4,14], Durkin K[4,14], Baete SH[4,12,13], Boada FE[4,15,16], Genfi A[4,14], Autea J[5,2,3,4], Newman J[4,14], Oathes DJ[17], Lindley SE[5,3], Abu-Amara D[4,14], Arnow BA[5], Crossley N[18,19], Hallmayer J[5,2,3], Fossati S[4,14], Rothbaum BO[20], Marmar CR[4,14], Bullmore ET[7,21,22], O'Hara R[5,3].

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A mechanistic understanding of the pathology of psychiatric disorders has been hampered by extensive heterogeneity in biology, symptoms, and behavior within diagnostic categories that are defined subjectively. We investigated whether leveraging individual differences in information-processing impairments in patients with post-traumatic stress disorder (PTSD) could reveal phenotypes within the disorder. We found that a subgroup of patients with PTSD from two independent cohorts displayed both aberrant functional connectivity within the ventral attention network (VAN) as revealed by functional magnetic resonance imaging (fMRI) neuroimaging and impaired verbal memory on a word list learning task. This combined phenotype was not associated with differences in symptoms or comorbidities, but nonetheless could be used to predict a poor response to psychotherapy, the best-validated treatment for PTSD. Using concurrent focal noninvasive transcranial magnetic stimulation and electroencephalography, we then identified alterations in neural signal flow in the VAN that were evoked by direct stimulation of that network. These alterations were associated with individual differences in functional fMRI connectivity within the VAN. Our findings define specific neurobiological mechanisms in a subgroup of patients with PTSD that could contribute to the poor response to psychotherapy.

The Parkinson's phenome-traits associated with Parkinson's disease in a broadly phenotyped cohort.

Heilbron K[1], Noyce AJ[2,3], Fontanillas P[1], Alipanahi B[1], Nalls MA[4,5]; 23andMe Research Team, Cannon P[1].

Collaborators: (24): Agee M, Auton A, Bell RK, Bryc K, Elson SL, Furlotte NA, Hinds DA, McCreight JC, Huber KE, Kleinman A, Litterman NK, McIntyre MH, Mountain JL, Noblin ES, Northover CAM, Pitts SJ, Sathirapongsasuti JF, Sazonova OV, Shelton JF, Shringarpure S, Tian C, Tung JY, Vacic V, Wilson CH.

NPJ Parkinsons Dis. **2019 Mar 27**;5:4. doi: 10.1038/s41531-019-0077-5. PMCID: PMC6437217. PMID: 30937360. eCollection 2019.

In order to systematically describe the Parkinson's disease phenome, we performed a series of 832 cross-sectional case-control analyses in a large database. Responses to 832 online survey-based phenotypes including diseases, medications, and environmental exposures were analyzed in 23andMe research participants. For each phenotype, survey respondents were used to construct a cohort of Parkinson's disease cases and age-matched and sex-matched controls, and an association test was performed using logistic regression. Cohorts included a median of 3899 Parkinson's disease cases and 49,808 controls, all of European ancestry. Highly correlated phenotypes were removed and the novelty of each significant association was systematically assessed (assigned to one of four categories: known, likely, unclear, or novel). Parkinson's disease diagnosis was associated with 122 phenotypes. We replicated 27 known associations and found 23 associations with a strong a priori link to a known association. We discovered 42 associations that have not previously been reported. Migraine, obsessive-compulsive disorder, and seasonal allergies were associated with Parkinson's disease and tend to occur decades before the typical age of diagnosis for Parkinson's disease. The phenotypes that currently comprise the Parkinson's disease phenome have mostly been explored in relatively small purpose-built studies. Using a single large dataset, we have successfully reproduced many of these established associations and have extended the Parkinson's disease phenome by discovering novel associations. Our work paves the way for studies of these associated phenotypes that explore shared molecular mechanisms with Parkinson's disease, infer causal relationships, and improve our ability to identify individuals at high-risk of Parkinson's disease.

OTHER RESEARCH OF INTEREST (Continued)

A Long-Term, Open-label Study to Evaluate the Safety and Tolerability of Brexpiprazole as Adjunctive Therapy in Adults With Major Depressive Disorder.

Hobart M, Zhang P, Skuban A, Brewer C, Hefting N[1], Sanchez R, McQuade RD.

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BACKGROUND: Long-term treatment is recommended in major depressive disorder (MDD) to prevent relapse and to restore functioning. The aim of this study (Orion; NCT01360866) was to assess the long-term safety, tolerability, and efficacy of open-label treatment with adjunctive brexpiprazole in adult patients with MDD.

METHODS: Patients rolled over into this 52-week study (amended to 26 weeks) from 3 randomized, double-blind, placebo-controlled studies. Patients received brexpiprazole 0.5 to 3 mg/d (flexible dose) adjunct to their current antidepressant treatment. The primary outcome variable was the frequency and severity of treatment-emergent adverse events (TEAEs). Efficacy was assessed as a secondary objective using clinical rating scales.

RESULTS: A total of 2944 patients were enrolled (1547 for 52 weeks, 1397 for 26 weeks), of whom 1895 (64.4%) completed the study. The TEAEs with incidence of 5% or greater were weight increase (17.7%), somnolence (8.0%), headache (7.2%), akathisia (6.7%), increased appetite (6.3%), insomnia (6.3%), fatigue (6.1%), viral upper respiratory tract infection (5.4%), and anxiety (5.2%). Most TEAEs were mild or moderate in severity. The mean increase in body weight was 2.7 kg to week 26 and 3.2 kg to week 52; 25.8% of patients had a weight increase of 7% or greater at any postbaseline visit. There were no clinically relevant findings related to extrapyramidal symptoms, prolactin, lipids, or glucose. Patients' symptoms and functioning showed continual improvement.

CONCLUSIONS: Adjunctive treatment with open-label brexpiprazole 0.5 to 3 mg/d was generally well tolerated for up to 52 weeks in patients with MDD and was associated with continued improvement in efficacy measures and functional outcomes.

Autonomic neurophysiologic implications of disorders comorbid with bladder pain syndrome vs myofascial pelvic pain.

Chelimsky GG[1], Yang S[2], Sanses T[3], Tatsuoka C[2], Buffington CAT[4], Janata J[5], McCabe P[2], Dombroski MA[6], Ialacci S[2], Hijaz A[7], Mahajan S[7], Zolnoun D[8], Chelimsky TC[9].

Neurourol Urodyn. **2019 Apr 4**. doi: 10.1002/nau.23995. PMID: 30945780. [Epub ahead of print]

AIMS: The neuropathophysiology of a debilitating chronic urologic pain condition, bladder pain syndrome (BPS), remains unknown. Our recent data suggests withdrawal of cardiovagal modulation in subjects with BPS, in contrast to sympathetic nervous system dysfunction in another chronic pelvic pain syndrome, myofascial pelvic pain (MPP). We evaluated whether comorbid disorders differentially associated with BPS vs MPP shed additional light on these autonomic differences.

METHODS: We compared the presence and relative time of onset of 27 other medical conditions in women with BPS, MPP, both syndromes, and healthy subjects. Analysis included an adjustment for multiple comparisons.

RESULTS: Among 107 female subjects (BPS alone = 32; BPS with MPP = 36; MPP alone = 9; healthy controls = 30), comorbidities differentially associated with BPS included irritable bowel syndrome (IBS), dyspepsia, and chronic nausea, whereas those associated with MPP included migraine headache and dyspepsia, consistent with the distinct autonomic neurophysiologic signatures of the two disorders. PTSD (earliest), anxiety, depression, migraine headache, fibromyalgia, chronic fatigue, and IBS usually preceded BPS or MPP. PTSD and the presence of both pelvic pain disorders in the same subject correlated with significantly increased comorbid burden.

CONCLUSIONS: Our study suggests a distinct pattern of comorbid conditions in women with BPS. These findings further support our hypothesis of primary vagal defect in BPS as compared with primary sympathetic defect in MPP, suggesting a new model for chronic these pelvic pain syndromes. Chronologically, PTSD, migraine, dysmenorrhea, and IBS occurred early, supporting a role for PTSD or its trigger in the pathophysiology of chronic pelvic pain.

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