GULF WAR ILLNESS

Helpful ways providers can communicate about persistent medically unexplained physical symptoms.

Anastasides N[1], Chiusano C[1], Gonzalez C[1], Graff F[1], Litke DR[1,2], McDonald E[1], Presnall-Shvorin J[1], Sullivan N[1], Quigley KS[3,4], Pigeon WR[5], Helmer DA[1], Santos SL[1], McAndrew LM[6,7].

BMC Fam Pract. **2019 Jan 16**;20(1):13. doi: 10.1186/s12875-018-0881-8. PMID: 30651073.

BACKGROUND: Communication between patients and providers about persistent "medically unexplained" physical symptoms (MUS) is characterized by discordance. While the difficulties are well documented, few studies have examined effective communication. We sought to determine what veterans with Gulf War Illness (GWI) perceive as the most helpful communication from their providers. Veterans with GWI, a type of MUS, have historically had complex relationships with medical providers. Determining effective communication for patients with particularly complex relationships may help identify the most critical communication elements for all patients with MUS.

METHODS: Two hundred and-ten veterans with GWI were asked, in a written questionnaire, what was the most useful thing a medical provider had told them about their GWI. Responses were coded into three categories with 10 codes.

RESULTS: The most prevalent helpful communication reported by patients was when the provider offered acknowledgement and validation (N = 70). Specific recommendations for managing GWI or its symptoms (N = 48) were also commonly reported to be helpful. In contrast, about a third of the responses indicated that nothing about the communication was helpful (N = 63). There were not differences in severity of symptoms, disability or healthcare utilization between patients who found acknowledgement and validation, specific recommendations or nothing helpful.

CONCLUSIONS: Previous research has documented the discord between patients and providers regarding MUS. This study suggests that most patients are able to identify something helpful a provider has said, particularly acknowledgement and validation and specific treatment recommendations. The findings also highlight missed communication opportunities with a third of patients not finding anything helpful.

CHRONIC FATIGUE SYNDROME

No Updates this Week for Chronic Fatigue Syndrome.

HEADACHE and MIGRAINE

Analysis of HCRTR2 Gene Variants and Cluster Headache in Sweden.

Fourier C[1], Ran C[1], Steinberg A[2], Sjöstrand C[2], Waldenlind E[2], Belin AC[1].

Headache. **2019 Jan 16**. doi: 10.1111/head.13462. PMID: 30652302. [Epub ahead of print]

OBJECTIVE: The purpose of this study was to investigate the HCRTR2 gene variants rs3122156, rs2653342, and rs2653349 in a large homogenous Swedish case-control cohort in order to further evaluate the possible contribution of HCRTR2 to cluster headache.

BACKGROUND: Cluster headache is a severe neurovascular disorder and the pathophysiology is not yet fully understood. Due to striking circadian and circannual patterns of this disease, the hypothalamus has been a research focus in cluster headache. Several studies with many different cohorts from Europe have investigated the hypocretin receptor 2 (HCRTR2) gene, which is expressed in the hypothalamus. In particular, one HCRTR2 single nucleotide polymorphism, rs2653349, has been subject to a number of genetic association studies on cluster headache, with conflicting results. Two other HCRTR2 gene variants, rs2653342 and rs2653349, have been reported to be linked to cluster headache in an Italian study.

METHODS: We genotyped a total of 517 patients diagnosed with cluster headache and 581 controls, representing a general Swedish population, for rs3122156, rs2653342, and rs2653349 using quantitative real-time PCR. Statistical analyses of genotype, allele, and haplotype frequencies for the 3 gene variants were performed comparing patients and controls.

RESULTS: For rs3122156, the minor allele frequency in patients was 25.9% compared to 29.9% in controls (P = .0421). However, this significance did not hold after correction for multiple testing. The minor allele frequencies for rs2653342 (14.7% vs 14.7%) and rs2653349 (19.5% vs 18.8%) were similar for patients and controls. Furthermore, we found one haplotype that was significantly less common in patients than controls (P = .0264). This haplotype included the minor allele for rs3122156 and the major alleles for rs2653342 and rs2653349. Significance did not hold after applying a permutation test.

CONCLUSIONS: Our data show a trend for association between cluster headache and the HCRTR2 polymorphism rs3122156, where the minor allele seems to be a protective factor. However, the other 2 HCRTR2 gene variants, including the previously reported rs2653349, were not associated with cluster headache in our Swedish material. A comparison with previous studies points to variance in genotype and allele frequencies among the different populations, which most likely contributes to the opposing results regarding rs2653349. Although the results from this study do not strongly support an association, HCRTR2 remains an interesting candidate gene for involvement in the pathophysiology of cluster headache.

HEADACHE and MIGRAINE (Continued)

Impact of migraine on health care utilization and expenses in obese adults: a US population-based study.

Wu J[1], Davis-Ajami ML[2], Lu ZK[3].

Clinicoecon Outcomes Res. **2018 Dec 31**;11:51-59. doi: 10.2147/CEOR.S189699. PMCID: PMC6318707. PMID: 30643442.eCollection 2019.

Purpose: Migraine prevalence increases in people with obesity, and obesity may contribute to migraine chronicity. Yet, few studies examine the effect of comorbid migraine on health care utilization and expenses in obese US adults. This study aimed to identify risk factors for migraine and compare the use of health care services and expenses between migraineurs and non-migraineurs in obese US adults.

Subjects and Methods: This 7-year retrospective study used longitudinal panel data from 2006 to 2013 from the Household Component of the Medical Expenditure Panel Survey to identify obese adults reporting migraines. Outcomes compared in migraineurs vs non-migraineurs were as follows: annualized per-person medical care, prescription drug, and total health expenses.

Results: In 23,596 obese adults, 4.7% reported migraine (n=1,025) approximating 3 million civilian noninstitutionalized US individuals. Logistic regression showed that the following sociodemographic characteristics increased migraine risk: age (18-45 years), females, White race, poor perceived health status, and greater Charlson comorbidity index. Migraineurs showed US$1,401 (*P*=0.007), US$813 (*P*<0.001), and US$2,213 (*P*=0.001) greater annual medical, prescription drug, and total health expenses than non-migraineurs, respectively. After adjustment, total health expenses increased by 31.6% in migraineurs vs non-migraineurs.

Conclusion: In this US adult obese population, migraineurs showed greater total health care utilization and expenses than non-migraineurs. Treatment plans that address risk factors associated with migraine and comorbidities may help reduce the utilization of health care services and costs.

[Healthcare behavior of migraine and headache patients when treatment is accompanied by the digital migraine app].

[Article in German]

Göbel H[1], Frank B[2], Heinze A[2], Zimmermann W[2], Göbel C[2,3], Göbel A[2,3], Brunkhorst J[4], Rupp K[5].

Schmerz. **2019 Jan 16**. doi: 10.1007/s00482-018-0355-x. PMID: 30649625. [Epub ahead of print]

BACKGROUND: Tension-type headache and migraine are the second and third most prevalent disorders of mankind worldwide, after dental caries. The widespread implementation of smartphones enables the use of specific software applications (apps) for digital treatment accompaniment. In this study, the use of the migraine app (Migräne-App) for iOS and Android was examined in the practical treatment of migraine and headache patients in an extensive population sample.

METHODS: An online survey was developed for the analysis of experiences as part of the treatment accompaniment and app usage. It contains questions concerning sociodemographic variables, the course of headache disorders and the previous treatment as well as the usage of the migraine app. The survey establishes compliance to the recommended treatment, the treatment plan, and treatment rules devised by the treating physician. The data collected were compared to traditional pen and paper documentation, prior to using the migraine app.

RESULTS: A total of 1464 users participated in the standardized survey. The average age was 47.19 ± 11.37 years (87.4% female, 12.5% male). On average, users suffered from headaches for 27.28 ± 13.6 years. The majority (76.5%) were cared for by a general practitioner. Of the users 70.9% reported that they presented the aggregated data from the app to their physician on consultation, 76.4% reported that the migraine app helped them to adhere to the treatment plan designed together with their physician and the rules about headache therapy. It showed both a highly significant reduction of headache days per months prior to usage (13.30 ± 7.45 days) in comparison to at the time of conducting the survey (10.03 ± 7.30 days) as well as a highly significant reduction of intake of acute medication (before 7.61 ± 5.58 vs. ongoing 6.78 ± 4.72 days).

CONCLUSION: The data show that the digital treatment control for therapy decisions made by the physician is highly relevant and established. Therapy compliance is improved and possible complications such as headache due to medication overuse are reduced. At the same time, a significant improvement of headache parameters and a marked overall improvement of treatment quality, amongst other things due to more easily available information and self-help tools can be observed.

HEADACHE and MIGRAINE (Continued)

STOP 101: A Phase 1, Randomized, Open-Label, Comparative Bioavailability Study of INP104, Dihydroergotamine Mesylate (DHE) Administered Intranasally by a I123 Precision Olfactory Delivery (POD®) Device, in Healthy Adult Subjects.

Shrewsbury SB[1], Jeleva M[1], Satterly KH[1], Lickliter J[2], Hoekman J[1].

Headache. **2019 Jan 19**. doi: 10.1111/head.13476. PMID: 30659611. [Epub ahead of print]

OBJECTIVE: Investigate the safety and pharmacokinetics (PK) of INP104, intranasal dihydroergotamine mesylate (DHE) administered via a Precision Olfactory Delivery (POD®) device, (Impel NeuroPharma, Seattle, WA) vs intravenous (IV) DHE and DHE nasal spray (Migranal®) in healthy adult subjects.

METHODS: This was a Phase 1, open-label, randomized, single-dose, 3-period, 3-way crossover study. Subjects received a single dose of A) INP104 1.45 mg (a drug-device combination product composed of DHE and the I123 POD device); B) DHE 45® Injection (IV) 1.0 mg; and C) DHE by Migranal® Nasal Spray 2.0 mg. Plasma levels of DHE and the major bioactive metabolite, 8'OH-DHE, were measured, and PK parameters were determined for both. Comparative bioavailability (BA) was assessed by calculating the ratio of the geometric means between treatments for C_{max} and $AUC_{0\text{-}inf}$ on the ln-transformed data. Safety was assessed from adverse events, vital signs, electrocardiograms, and clinical laboratory values.

RESULTS: Thirty-eight subjects were enrolled, 36 were dosed with at least 1 IP and 27 were included in the evaluation of PK and comparative BA. DHE plasma levels following INP104 1.45 mg administration reached 93% of C_{max} by 20 minutes and were comparable to IV DHE 1.0 mg by 30 minutes (1219 ng/mL for INP104 vs 1224 ng/mL for IV DHE), which was the T_{max} for INP104. From 30 minutes onward, DHE levels for INP104 closely matched those of IV DHE to 48 hours, the last time point measured. In comparison, the C_{max} for Migranal was 299.6 pg/mL (approximately 4-fold less than INP104) and occurred at 47 minutes, 17 minutes later than INP104. Plasma DHE $AUC_{0\text{-}inf}$ were 6275, 7490, and 2199 h*pg/mL for INP104, IV DHE, and Migranal, respectively. Variability (coefficient of variation [CV%]) for C_{max} and $AUC_{0\text{-}inf}$ for INP104 compared to Migranal indicated more consistent delivery with INP104. In the BA comparison using the PK population (subjects who had received all 3 treatments), the ratios of geometric means (percent) for C_{max} and $AUC_{0\text{-}inf}$ were 7.9% and 74.2%, respectively, for INP104: IV DHE, and 445% and 308% for INP104: Migranal. Mean plasma concentration profiles for 8'-OH-DHE were proportionately lower and followed a similar profile to the parent compound, regardless of route of administration (IN vs IV) or delivery system (Migranal vs INP104). Treatment emergent AEs (TEAEs), of mostly mild intensity, were reported by 15/31 (48.4%), 21/32 (65.6%), and 14/34 (41.2%) subjects after INP104, IV DHE, and Migranal, respectively. Treatment-related TEAEs occurred in 6/31 (19.4%), 16/32 (50.0%), and 4/34 (11.8%) subjects after INP104, IV DHE, and Migranal, respectively.

CONCLUSION: INP104 met the predefined statistical criteria for comparative bioavailability with IV DHE and Migranal. The shorter time to reach C_{max} and at 4 times the plasma concentration of DHE in comparison to Migranal combined with a favorable tolerability profile support further investigation of INP104 as an effective, well tolerated, and non-invasive treatment for acute episodic migraine.

CHRONIC PAIN

Addressing the Opioid Epidemic in the United States: Lessons From the Department of Veterans Affairs.

Gellad WF[1], Good CB[1], Shulkin DJ[2].

JAMA Intern Med. **2017 May 1**;177(5):611-612. doi: 10.1001/jamainternmed.2017.0147. PMID: 28288245.

[Note: Delayed PubMed posting of *JAMA* 2017 Article.] [Link to JAMA Viewpoint article.]

Over the past 15 years, more than 165 000 people in the United States have died from overdoses related to prescription opioids, and millions more have suffered adverse consequences. The misuse and abuse of prescription opioids have contributed to a precipitous increase in heroin and fentanyl overdoses.

Patients treated in the health care system of the Department of Veterans Affairs (VA) are part of this epidemic. Chronic pain impacts half of veterans using the VA, complicated by high rates of psychiatric comorbidities such as substance use disorder and posttraumatic stress disorder. In 2009, the VA established a national office to coordinate and improve pain management practices, and in 2011, developed standardized metrics for opioid use across the system. Nonetheless, by 2012, nearly 25% of veterans receiving outpatient care in the VA were receiving an opioid.

In 2013, the VA launched the Opioid Safety Initiative (OSI), the first of several system-wide initiatives to address opioid overuse. By leveraging the department's data capabilities and organization, these initiatives reduced the use of opioid medications and improved the safety of opioid prescribing, while expanding alternative pain therapies. By mid-2016 compared with mid-2012, the number of veterans dispensed an opioid each quarter had decreased by 172 000, or about 25%. Moreover, there were 57 000 (47%) fewer patients receiving concomitant opioids and benzodiazepines and 22 000 (36%) fewer patients receiving daily opioid dosages of more than 100 morphine-milligram equivalents, both measures of potentially unsafe opioid use. Between 2010 and 2015, the rate of opioid overdose among veterans dispensed a prescription opioid, measured using ICD-9 codes from health care visits, decreased from 0.16% to 0.08%.

The VA's efforts to address the opioid epidemic can inform other health care systems planning comprehensive action to reduce the risks associated with opioid therapy. We describe the efforts and the lessons learned.

CHRONIC PAIN (Continued)

Coverage of Nonpharmacologic Treatments for Low Back Pain Among US Public and Private Insurers.

Heyward J[1,2], Jones CM[3], Compton WM[4], Lin DH[1,2], Losby JL[5], Murimi IB[1,2], Baldwin GT[5], Ballreich JM[1,6], Thomas DA[4], Bicket MC[1, 7], Porter L[8], Tierce JC[1,2], Alexander GC[1,2,9].

JAMA Netw Open. **2018 Oct 5**;1(6):e183044. doi: 10.1001/jamanetworkopen.2018.3044. PMID: 30646222.

[Note: Delayed PubMed posting of *JAMA* 2018 Health Policy Article.]

Importance: Despite epidemic rates of addiction and death from prescription opioids in the United States, suggesting the importance of providing alternatives to opioids in the treatment of pain, little is known regarding how payers' coverage policies may facilitate or impede access to such treatments.

Objective: To examine coverage policies for 5 nonpharmacologic approaches commonly used to treat acute or chronic low back pain among commercial and Medicare Advantage insurance plans, plus an additional 6 treatments among Medicaid plans.

Design, Setting, and Participants: Cross-sectional study of 15 commercial, 15 Medicaid, and 15 Medicare Advantage health plans for the 2017 calendar year in 16 states representing more than half of the US population. Interviews were conducted with 43 senior medical and pharmacy health plan executives from representative plans.

Main Outcomes and Measures: Medical necessity and coverage status for the treatments examined, as well as the use of utilization management tools and cost-sharing magnitude and structure.

Results: Commercial and Medicare insurers consistently regarded physical and occupational therapy as medically necessary, but policies varied for other therapies examined. Payers most commonly covered physical therapy (98% [44 of 45 plans]), occupational therapy (96% [43 of 45 plans]), and chiropractic care (89% [40 of 45 plans]), while transcutaneous electrical nerve stimulation (67% [10 of 15 plans]) and steroid injections (60% [9 of 15 plans]) were the most commonly covered among the therapies examined for Medicaid plans only. Despite evidence in the literature to support use of acupuncture and psychological interventions, these therapies were either not covered by plans examined (67% of all plans [30 of 45] did not cover acupuncture) or lacked information about coverage (80% of Medicaid plans [12 of 15] lacked information about coverage of psychological interventions). Utilization management tools, such as prior authorization, were common, but criteria varied greatly with respect to which conditions and what quantity and duration of services were covered. Interviewees represented 6 Medicaid managed care organizations, 2 Medicare Advantage or Part D plans, 9 commercial plans, and 3 trade organizations (eg, Blue Cross Blue Shield Association). Interviews with plan executives indicated a low level of integration between the coverage decision-making processes for pharmacologic and nonpharmacologic therapies for chronic pain.

Conclusions and Relevance: Wide variation in coverage of nonpharmacologic treatments for low back pain may be driven by the absence of best practices, the administrative complexities of developing and revising coverage policies, and payers' economic incentives. Such variation suggests an important opportunity to improve the accessibility of services, reduce opioid use, and ultimately improve the quality of care for individuals with chronic, noncancer pain while alleviating the burden of opioid addiction and overdose.

CHRONIC PAIN (Continued)

Patterns of Immediate-Release and Extended-Release Opioid Analgesic Use in the Management of Chronic Pain, 2003-2014.

Hwang CS[1,2], Kang EM[2,3], Ding Y[2], Ocran-Appiah J[2,4], McAninch JK[2], Staffa JA[2], Kornegay CJ[2], Meyer TE[2].

JAMA Netw Open. **2018 Jun 1**;1(2):e180216. doi: 10.1001/jamanetworkopen.2018.0216. PMID: 30646061.

[Note: Delayed PubMed posting of *JAMA* 2018 Public Health Article.]

Importance: Many stakeholders are working to improve the safe use of immediate-release (IR) and extended-release/long-acting (ER/LA) opioid analgesics. However, little information exists regarding the relative use of these 2 formulations in chronic pain management.

Objectives: To describe the distribution of IR and ER/LA opioid analgesic therapy duration and examine adding and switching patterns among patients receiving long-term IR opioid analgesic therapy, defined as at least 90 consecutive days of IR formulation use.

Design, Setting, and Participants: A retrospective cohort study of 169 million individuals receiving opioid analgesics from across 90% of outpatient retail pharmacies in the United States from January 1, 2003, to December 31, 2014, using the IQVIA Health Vector One: Data Extract Tool. Analyses were conducted from March 2015 to June 2017.

Exposures: Receipt of dispensed IR or ER/LA opioid analgesic prescription.

Main Outcomes and Measures: Distribution of therapy frequency and duration of IR and ER/LA opioid analgesic use, and annual proportions of patients receiving long-term IR opioid analgesic therapy who added an ER/LA formulation while continuing to use an IR formulation, switched to an ER/LA formulation, or continued receiving IR opioid analgesic therapy only.

Results: Among the 169 280 456 patients included in this analysis, 168 315 458 patients filled IR formulations and 10 216 570 patients filled ER/LA formulations. A similar percentage of women received ER/LA (55%) and IR (56%) formulations, although those receiving ER/LA formulations (72%) were more likely to be aged 45 years or older compared with those receiving IR formulations (46%). The longest opioid analgesic episode duration was 90 days or longer for 11 563 089 patients (7%) filling IR formulations and 3 103 777 patients (30%) filling ER/LA formulations. The median episode duration was 5 days (interquartile range, 3-10 days) for patients using IR formulations and 30 days (interquartile range, 21-74 days) for patients using ER/LA formulations. From January 1, 2003, to December 31, 2014, a small and decreasing proportion of patients with long-term IR opioid analgesic therapy added (3.8% in 2003 to 1.8% in 2014) or switched to (1.0% in 2003 to 0.5% in 2014) an ER/LA formulation.

Conclusions and Relevance: Most patients receiving opioid analgesics, whether for short or extended periods, use IR formulations. Once receiving long-term IR opioid analgesic therapy, patients are unlikely to add or switch to an ER/LA formulation.

CHRONIC PAIN (Continued)

Genome-wide meta-analysis of 158,000 individuals of European ancestry identifies three loci associated with chronic back pain.

Suri P[1,2,3], Palmer MR[4], Tsepilov YA[5,6,7], Freidin MB[8], Boer CG[9], Yau MS[10,11], Evans DS[12], Gelemanovic A[13], Bartz TM[14,15], Nethander M[16], Arbeeva L[17], Karssen L[5], Neogi T[18], Campbell A[19], Mellstrom D[20], Ohlsson C[21], Marshall LM[22], Orwoll E[23], Uitterlinden A[9], Rotter JI[24,25], Lauc G[26, 27], Psaty BM[14,28,29,30], Karlsson MK[31], Lane NE[32], Jarvik GP[4,33], Polasek O[13,34], Hochberg M[35], Jordan JM[17], Van Meurs JBJ[9], Jackson R[36], NielsonCM[37], Mitchell BD[35, 38], Smith BH[39], Hayward C[40], Smith NL[1,29,30], Aulchenko YS[5], Williams FMK[8].

PLoS Genet. **2018 Sep 27**;14(9):e1007601. doi: 10.1371/journal.pgen.1007601. PMCID: PMC6159857. PMID: 30261039. eCollection 2018 Sep.

[Note: Delayed PubMed posting of *PLoS Genetics* 2018 Research Article.]

Back pain is the #1 cause of years lived with disability worldwide, yet surprisingly little is known regarding the biology underlying this symptom. We conducted a genome-wide association study (GWAS) meta-analysis of chronic back pain (CBP). Adults of European ancestry were included from 15 cohorts in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium, and from the UK Biobank interim data release. CBP cases were defined as those reporting back pain present for ≥3-6 months; non-cases were included as comparisons ("controls"). Each cohort conducted genotyping using commercially available arrays followed by imputation. GWAS used logistic regression models with additive genetic effects, adjusting for age, sex, study-specific covariates, and population substructure. The threshold for genome-wide significance in the fixed-effect inverse-variance weighted meta-analysis was p<5×10(-8). Suggestive (p<5×10(-7)) and genome-wide significant (p<5×10(-8)) variants were carried forward for replication or further investigation in the remaining UK Biobank participants not included in the discovery sample. The discovery sample comprised 158,025 individuals, including 29,531 CBP cases. A genome-wide significant association was found for the intronic variant rs12310519 in SOX5 (OR 1.08, p = 7.2×10(-10)). This was subsequently replicated in 283,752 UK Biobank participants not included in the discovery sample, including 50,915 cases (OR 1.06, p = 5.3×10(-11)), and exceeded genome-wide significance in joint meta-analysis (OR 1.07, p = 4.5×10(-19)). We found suggestive associations at three other loci in the discovery sample, two of which exceeded genome-wide significance in joint meta-analysis: an intergenic variant, rs7833174, located between CCDC26 and GSDMC (OR 1.05, p = 4.4×10(-13)), and an intronic variant, rs4384683, in DCC (OR 0.97, p = 2.4×10(-10)). In this first reported meta-analysis of GWAS for CBP, we identified and replicated a genetic locus associated with CBP (SOX5). We also identified 2 other loci that reached genome-wide significance in a 2-stage joint meta-analysis (CCDC26/GSDMC and DCC).

OTHER RESEARCH OF INTEREST

Child abuse interacts with hippocampal and corpus callosum volume on psychophysiological response to startling auditory stimuli in a sample of veterans.

Young DA[1], Neylan TC[2], Chao LL[3], O'Donovan A[4], Metzler TJ[5], Inslicht SS[6].

J Psychiatr Res. **2019 Jan** 11;111:16-23. doi: 10.1016/j.jpsychires.2019.01.011. PMID: 30660809. [Epub ahead of print]

Child abuse (CA), which is linked to posttraumatic stress disorder (PTSD), has been associated with a reduction in both hippocampal and corpus callosum (CC) volume. However, few studies have explored these relationships on psychophysiological variables related to trauma exposure. Therefore, we assessed whether the interaction between CA and hippocampal and CC volume were associated with enhanced fear potentiated psychophysiological response patterns in a sample of Veterans. 147 Veteran participants who were part of a larger study of Gulf War Illness were exposed to startling sounds in no, ambiguous, and high threat conditions and also provided MRI data. The Clinician Administered PTSD Scale and Trauma History Questionnaire were used to measure PTSD and CA respectively. Psychophysiological response was measured by EMG, SCR, and heart rate. Repeated-measures mixed linear models were used to assess the significance of CA by neural structure interactions. CA interacted with both hippocampal and CC volume on psychophysiological response magnitudes, where participants with CA and smaller hippocampal volume had greater EMG ($p < 0.01$) and SCR ($p < 0.05$) magnitudes across trials and over threat conditions. Participants with CA and smaller CC volume had greater SCR magnitudes across trials and over threat conditions ($p < 0.01$). Hippocampal and genu volume mediated CA and psychophysiological response magnitude. CA may impact psychophysiological response via a reduction in hippocampal and CC volume. Volumetric reduction in these structures may indicate a neurofunctional, CA-related increase in threat sensitivity, which could portend increased PTSD susceptibility and adverse interpersonal and social consequences across the lifespan.

OTHER RESEARCH OF INTEREST (Continued)

Secreted amyloid-β precursor protein functions as a $GABA_BR1a$ ligand to modulate synaptic transmission.

Rice HC[1,2], de Malmazet D[3,4], Schreurs A[5], Frere S[6], Van Molle I[7], Volkov AN[7,8], Creemers E[1,2], Vertkin I[6], Nys J[1,2], Ranaivoson FM[9], Comoletti D[9,10], Savas JN[11], Remaut H[7], Balschun D[5], Wierda KD[1,2], Slutsky I[6], Farrow K[3,4,12,13], De Strooper B[14,2,15], de Wit J[14,2].

Science. **2019 Jan 11**;363(6423). pii: eaao4827. doi: 10.1126/science.aao4827. PMID: 30630900.

Amyloid-β precursor protein (APP) is central to the pathogenesis of Alzheimer's disease, yet its physiological function remains unresolved. Accumulating evidence suggests that APP has a synaptic function mediated by an unidentified receptor for secreted APP (sAPP). Here we show that the sAPP extension domain directly bound the sushi 1 domain specific to the γ-aminobutyric acid type B receptor subunit 1a ($GABA_BR1a$). sAPP-$GABA_BR1a$ binding suppressed synaptic transmission and enhanced short-term facilitation in mouse hippocampal synapses via inhibition of synaptic vesicle release. A 17-amino acid peptide corresponding to the $GABA_BR1a$ binding region within APP suppressed in vivo spontaneous neuronal activity in the hippocampus of anesthetized Thy1-GCaMP6s mice. Our findings identify $GABA_BR1a$ as a synaptic receptor for sAPP and reveal a physiological role for sAPP in regulating $GABA_BR1a$ function to modulate synaptic transmission.

Association of body mass index and waist-to-hip ratio with brain structure: UK Biobank study.

Hamer M[1], Batty GD[2].

Neurology. **2019 Jan 9**. pii: 10.1212/WNL.0000000000006879. doi: 10.1212/WNL.0000000000006879. PMID: 30626649. [Epub ahead of print]

OBJECTIVE: To examine the association of body mass index (BMI) and waist-to-hip ratio (WHR) with brain volume.

METHODS: We used cross-sectional data from the UK Biobank study (n = 9,652, age 55.4 ± 7.5 years, 47.9% men). Measures included BMI, WHR, and total fat mass as ascertained from bioimpedance. Brain images were produced with structural MRI.

RESULTS: After adjustment for a range of covariates, higher levels of all obesity measures were related to lower gray matter volume: BMI per 1 SD (β coefficient -4,113, 95% confidence interval [CI] -4,862 to -3,364), WHR (β coefficient -4,272, 95% CI -5,280 to -3,264), and fat mass (β coefficient -4,590, 95% CI -5,386 to -3,793). The combination of overall obesity (BMI ≥30 kg/m^2) and central obesity (WHR >0.85 for women, >0.90 for men) was associated with the lowest gray matter compared with that in lean adults. In hypothesis-free testing with a Bonferroni correction, obesity was also related to various regional brain volumes, including caudate, putamen, pallidum, and nucleus accumbens. No associations between obesity and white matter were apparent.

CONCLUSION: The combination of heightened BMI and WHR may be an important risk factor for gray matter atrophy.

Reduced non-rapid eye movement sleep is associated with tau pathology in early Alzheimer's disease.

Lucey BP[1,2], McCullough A[3], Landsness EC[4], Toedebusch CD[4], McLeland JS[4], Zaza AM[3], Fagan AM[4,2,5], McCue L[6], Xiong C[6], Morris JC[4,2,5], Benzinger TLS[3,5], Holtzman DM[1,2,5].

Sci Transl Med. **2019 Jan 9**;11(474). pii: eaau6550. doi: 10.1126/scitranslmed.aau6550. PMID: 30626715.

In Alzheimer's disease (AD), deposition of insoluble amyloid-β (Aβ) is followed by intracellular aggregation of tau in the neocortex and subsequent neuronal cell loss, synaptic loss, brain atrophy, and cognitive impairment. By the time even the earliest clinical symptoms are detectable, Aβ accumulation is close to reaching its peak and neocortical tau pathology is frequently already present. The period in which AD pathology is accumulating in the absence of cognitive symptoms represents a clinically relevant time window for therapeutic intervention. Sleep is increasingly recognized as a potential marker for AD pathology and future risk of cognitive impairment. Previous studies in animal models and humans have associated decreased non-rapid eye movement (NREM) sleep slow wave activity (SWA) with Aβ deposition. In this study, we analyzed cognitive performance, brain imaging, and cerebrospinal fluid (CSF) AD biomarkers in participants enrolled in longitudinal studies of aging. In addition, we monitored their sleep using a single-channel electroencephalography (EEG) device worn on the forehead. After adjusting for multiple covariates such as age and sex, we found that NREM SWA showed an inverse relationship with AD pathology, particularly tauopathy, and that this association was most evident at the lowest frequencies of NREM SWA. Given that our study participants were predominantly cognitively normal, this suggested that changes in NREM SWA, especially at 1 to 2 Hz, might be able to discriminate tau pathology and cognitive impairment either before or at the earliest stages of symptomatic AD.