## GULF WAR ILLNESS

### High-fidelity discrete modeling of the HPA axis: a study of regulatory plasticity in biology.

Sedghamiz H[1], Morris M[1], Craddock TJA[2,3], Whitley D[4], Broderick G[5,6].

BMC Syst Biol. **2018 Jul 17**;12(1):76. doi: 10.1186/s12918-018-0599-1. PMCID: PMC6050677. PMID: 30016990.

BACKGROUND: The hypothalamic-pituitary-adrenal (HPA) axis is a central regulator of stress response and its dysfunction has been associated with a broad range of complex illnesses including Gulf War Illness (GWI) and Chronic Fatigue Syndrome (CFS). Though classical mathematical approaches have been used to model HPA function in isolation, its broad regulatory interactions with immune and central nervous function are such that the biological fidelity of simulations is undermined by the limited availability of reliable parameter estimates.

METHOD: Here we introduce and apply a generalized discrete formalism to recover multiple stable regulatory programs of the HPA axis using little more than connectivity between physiological components. This simple discrete model captures cyclic attractors such as the circadian rhythm by applying generic constraints to a minimal parameter set; this is distinct from Ordinary Differential Equation (ODE) models, which require broad and precise parameter sets. Parameter tuning is accomplished by decomposition of the overall regulatory network into isolated sub-networks that support cyclic attractors. Network behavior is simulated using a novel asynchronous updating scheme that enforces priority with memory within and between physiological compartments.

RESULTS: Consistent with much more complex conventional models of the HPA axis, this parsimonious framework supports two cyclic attractors, governed by higher and lower levels of cortisol respectively. Importantly, results suggest that stress may remodel the stability landscape of this system, favoring migration from one stable circadian cycle to the other. Access to each regime is dependent on HPA axis tone, captured here by the tunable parameters of the multi-valued logic. Likewise, an idealized glucocorticoid receptor blocker alters the regulatory topology such that maintenance of persistently low cortisol levels is rendered unstable, favoring a return to normal circadian oscillation in both cortisol and glucocorticoid receptor expression.

CONCLUSION: These results emphasize the significance of regulatory connectivity alone and how regulatory plasticity may be explored using simple discrete logic and minimal data compared to conventional methods.

## CHRONIC FATIGUE SYNDROME

### Identification of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome-associated DNA methylation patterns.

Trivedi MS[1], Oltra E[2], Sarria L[3], Rose N[1], Beljanski V[4], Fletcher MA[3,5], Klimas NG[3,5], Nathanson L[3].

PLoS One. **2018 Jul 23**;13(7):e0201066. doi: 10.1371/journal.pone.0201066. PMID: 30036399. eCollection 2018.

BACKGROUND: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a complex condition involving multiple organ systems and characterized by persistent/relapsing debilitating fatigue, immune dysfunction, neurological problems, and other symptoms not curable for at least 6 months. Disruption of DNA methylation patterns has been tied to various immune and neurological diseases; however, its status in ME/CFS remains uncertain. Our study aimed at identifying changes in the DNA methylation patterns that associate with ME/CFS.

METHODS: We extracted genomic DNA from peripheral blood mononuclear cells from 13 ME/CFS study subjects and 12 healthy controls and measured global DNA methylation by ELISA-like method and site-specific methylation status using Illumina MethylationEPIC microarrays. Pyrosequencing validation included 33 ME/CFS cases and 31 controls from two geographically distant cohorts.

RESULTS: Global DNA methylation levels of ME/CFS cases were similar to those of controls. However, microarray-based approach allowed detection of 17,296 differentially methylated CpG sites in 6,368 genes across regulatory elements and within coding regions of genes. Analysis of DNA methylation in promoter regions revealed 307 differentially methylated promoters. Ingenuity pathway analysis indicated that genes associated with differentially methylated promoters participated in at least 15 different pathways mostly related to cell signaling with a strong immune component.

CONCLUSIONS: This is the first study that has explored genome-wide epigenetic changes associated with ME/CFS using the advanced Illumina MethylationEPIC microarrays covering about 850,000 CpG sites in two geographically distant cohorts of ME/CFS cases and matched controls. Our results are aligned with previous studies that indicate a dysregulation of the immune system in ME/CFS. They also suggest a potential role of epigenetic de-regulation in the pathobiology of ME/CFS. We propose screening of larger cohorts of ME/CFS cases to determine the external validity of these epigenetic changes in order to implement them as possible diagnostic markers in clinical setting.

## CHRONIC FATIGUE SYNDROME (Continued)

### Brain function characteristics of chronic fatigue syndrome: A task fMRI study.

Shan ZY[1], Finegan K[2], Bhuta S[2], Ireland T[2], Staines DR[1], Marshall-Gradisnik SM[1], Barnden LR[1].

Neuroimage Clin. **2018 Apr 25**;19:279-286. doi: 10.1016/j.nicl.2018.04.025. PMCID: PMC6051500. PMID: 30035022. eCollection 2018.

The mechanism underlying neurological dysfunction in chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is yet to be established. This study investigated the temporal complexity of blood oxygenation level dependent (BOLD) changes in response to the Stroop task in CFS patients. 43 CFS patients (47.4 ± 11.8 yrs) and 26 normal controls (NCs, 43.4 ± 13.9 yrs) were included in this study. Their mental component summary (MCS) and physical component summary (PCS) from the 36-item Short Form Health Survey (SF-36) questionnaire were recorded. Their Stroop colour-word task performance was measured by accuracy and response time (RT). The BOLD changes associated with the Stroop task were evaluated using a 2-level general linear model approach. The temporal complexity of the BOLD responses, a measure of information capacity and thus adaptability to a challenging environment, in each activated region was measured by sample entropy (SampEn). The CFS patients showed significantly longer RTs than the NCs ($P < 0.05$) but no significant difference in accuracy. One sample *t*-tests for the two groups (Family wise error adjusted $P_{FWE} < 0.05$) showed more BOLD activation regions in the CFS, although a two sample group comparison did not show significant difference. BOLD SampEns in ten regions were significantly lower (FDR-q < 0.05) in CFS patients. BOLD SampEns in 15 regions were significantly associated with PCS (FDR-q < 0.05) and in 9 regions were associated with MCS (FDR-q < 0.05) across all subjects. SampEn of the BOLD signal in the medioventral occipital cortex could explain 40% and 31% of the variance in the SF-36 PCS and MCS scores, and those in the precentral gyrus could explain an additional 16% and 7% across all subjects. This is the first study to investigate BOLD signal SampEn in response to tasks in CFS. The results suggest the brain responds differently to a cognitive challenge in patients with CFS, with recruitment of wider regions to compensate for lower information capacity.

## HEADACHE and MIGRAINE

### Identifying Natural Subgroups of Migraine Based on Comorbidity and Concomitant Condition Profiles: Results of the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study.

Lipton RB[1,2], Fanning KM[3], Buse DC[2], Martin VT[4], Reed ML[3], Manack Adams A[5], Goadsby PJ[6,7].

Headache. **2018 Jul 19**. doi: 10.1111/head.13342. PMID: 30024028. [Epub ahead of print]

OBJECTIVE: To identify natural subgroups of people with migraine based on profiles of comorbidities and concomitant conditions, hereafter referred to as comorbidities.

BACKGROUND: Migraine is a heterogeneous disease. Identifying natural subgroups (endophenotypes) may facilitate biological and genetic characterization and the development of personalized treatment.

METHODS: The Chronic Migraine Epidemiology and Outcomes Study is a prospective web-based survey study designed to characterize the course of migraine and related comorbidities in a systematic US sample of people with migraine. Respondents were asked if they ever had a specific comorbidity and, if present, whether the comorbidity was confirmed/diagnosed by a "doctor"; 62 comorbidities were available for analysis. Latent class analysis (LCA) modeling determined the optimal number of classes and a parsimonious set of comorbidities.

RESULTS: Of the 12,810 respondents with migraine, 11,837 reported ≥1 comorbidity and were included in this analysis. After statistical analysis and clinical judgment reduced the number of comorbidities, we selected an 8-class model based on 22 comorbidities. Each class had a distinct pattern summarized as follows: Class 1, Most Comorbidities; Class 2, Respiratory/Psychiatric; Class 3, Respiratory/Pain; Class 4, Respiratory; Class 5, Psychiatric; Class 6, Cardiovascular; Class 7, Pain; Class 8, Fewest Comorbidities. The distribution of individuals across models was variable, with one-third of respondents in Class 8 (Fewest Comorbidities) and <10% in Class 1 (Most Comorbidities). Demographic and headache characteristics, not used in assigning class membership, varied across classes. For example, comparing Class 1 (Most Comorbidities) and Class 8 (Fewest Comorbidities), Class 1 had a greater proportion of individuals with severe disability (Migraine Disability Assessment grade IV; 48.1% vs 22.3% of overall individuals) and higher rates of allodynia (67.6% vs 47.0%), medication overuse (36.4% vs 15.0%), chronic migraine (23.1% vs 9.1%), and aura (40.1% vs 28.8%).

CONCLUSIONS: LCA modeling identified 8 natural subgroups of persons with migraine based on comorbidity profiles. These classes show differences in demographic and headache features not used to form the classes. Subsequent research will assess prognostic and biologic differences among the classes.

## HEADACHE and MIGRAINE (Continued)

### Do Headache Patients Require More Care in Between Visits Than Other Neurology Outpatients?

Brilla R[1], Woo KM[2], Seeger SK[1].

Headache. **2018 Jul 19**. doi: 10.1111/head.13339. PMID: 30024044. [Epub ahead of print]

BACKGROUND: There is evidence that time spent in patient care in between patient visits is increasing and a contributor to physician burnout. The extent of this work on providers in the field of headache medicine is unknown.

OBJECTIVES: To establish whether headache outpatients require a high level of care in addition to clinic visits, based on the quantity of remote encounters per patient (phone calls and secure email communication to the clinics), in comparison to other neurologic clinics.

METHODS: In an academic referral clinic, a total of 3164 established patients were included in this retrospective analysis, 275 from the headache clinic, the remainder from various other neurology clinics (2 physician providers per clinic except 3 physician providers in the headache clinic). Patients presenting for a follow-up visit between January 2014 and April 2016 were observed for a 12-month period during which the number of a) telephone and b) secure email (MyChart) encounters per patient was recorded, and in addition, the number of entries related to each of these encounters. This analysis did not require IRB approval as per institutional guidelines.

RESULTS: Headache clinic patients required a high frequency of remote encounters (composite of both telephone and email messages) per patient, second only to the MS clinic patients. Use of secure email messaging (MyChart) per patient was much higher in the headache clinic compared to all other clinics.

CONCLUSION: Patients in a headache clinic in an academic tertiary care setting require a high intensity of remote outpatient care, more so than patients in other neurology subspecialty clinics and general neurology clinic, with the exception of the neuroimmunology/MS clinic. This is to a large extent secondary to the very frequent use of secure email linked to the electronic medical record by headache patients.

### Migraine and greater pain symptoms at 10-year follow-up among patients with major depressive disorder.

Hung CI[1], Liu CY[1], Yang CH[2], Wang SJ[3,4].

J Headache Pain. **2018 Jul 17**;19(1):56. doi: 10.1186/s10194-018-0884-9. PMID: 30019214.

BACKGROUND: No study has investigated the associations of migraine with pain symptoms over a ten-year period among outpatients with major depressive disorder (MDD). This study aimed to investigate this issue.

METHODS: At baseline, the study enrolled 290 outpatients with MDD and followed-up the patients at six-month, two-year, and ten-year time points. MDD and anxiety comorbidities were diagnosed using the Structured Clinical Interview for DSM-IV-text revision. Migraine was diagnosed based on the International Classification of Headache Disorders. The bodily pain subscale of the Short Form 36 (SF-BP) and the pain subscale (PS) of the Depression and Somatic Symptoms scale were also used. Generalized Estimating Equation models were employed to investigate the longitudinal impacts of migraine on pain symptoms.

RESULTS: MDD patients with migraine had lower SF-BP and higher PS scores than those without. Depression, anxiety, and headache indices were significantly correlated with SF-BP and PS scores. The higher the frequency of migraine, the more often patients suffered from pain symptoms. Patients with migraine at all investigated time points suffered from pain symptoms most of the time (ranging from 60.0% to 73.7%) over the 10 years. After controlling for depression and anxiety, migraine was independently associated with a decreased SF-BP score (by 8.93 points) and an increased PS score (by 1.33 points).

CONCLUSION: Migraine was an important comorbidity associated with greater severities of pain symptoms during long-term follow-up. Migraine treatment should be integrated into the treatment of depression to improve pain symptoms and quality of life in the pain dimension.

## CHRONIC PAIN

### Association of Pain after Trauma with Long-term Functional and Mental Health Outcomes.

Herrera-Escobar JP[1], Apoj M[2], Weed C[3], Harlow AF[1], Al Rafai SS[1], Lilley E[1], Kasotakis G[2], Brasel K[4], Kaafarani HM[5], Velmahos G[5], Salim A[6], Haider AH[1,6].

J Trauma Acute Care Surg. **2018 Jul 17**. doi: 10.1097/TA.0000000000002017. PMID: 30020227. [Epub ahead of print]

BACKGROUND: Chronic pain after trauma is associated with serious clinical, social, and economic burden. Due to limitations in trauma registry data and previous studies, the current prevalence of chronic pain after trauma is unknown, and little is known about the association of pain with other long-term outcomes. We sought to describe the long-term burden of self-reported pain after injury, and determine its association with positive screen for posttraumatic stress disorder (PTSD), functional status, and return to work.

METHODS: Trauma survivors with moderate or severe injuries and one completed follow-up interview at either 6- or 12-months post-injury were identified from the Functional Outcomes and Recovery after Trauma Emergencies (FORTE) project. Multivariable logistic regression models clustered by facility and adjusting for confounders were used to obtain the odds of positive PTSD screening, not returning to work, and functional limitation at 6- and 12-months after injury, in trauma patients who reported to have pain on a daily basis compared to those who did not.

RESULTS: We completed interviews on 650 patients (43% of eligible patients). Half of patients (50%) reported experiencing pain daily, and 23% reported taking pain medications daily between 6- and 12-months post-injury. Compared to patients without pain, patients with pain were more likely to screen positive for PTSD (OR: 5.12 [2.97-8.85]), have functional limitations for at least one daily activity (OR: 2.42 [1.38-4.26]), and not return to work (OR: 1.86 [1.02-3.39]).

CONCLUSIONS: There is a significant amount of self-reported chronic pain after trauma, which is in turn associated with positive screen for PTSD, functional limitations, and delayed return to work. New metrics for measuring successful care of the trauma patient are needed that span beyond mortality, and it is important we shift our focus beyond the trauma center and towards improving the long-term morbidity of trauma survivors. Level of Evidence Level III - Therapeutic/Care Management.

### Left DLPFC rTMS Reduces the Development of Long-Term Muscle Pain.

Seminowicz DA[1,2], de Martino E[3], Schabrun SM[4], Graven-Nielsen T[3].

Pain. **2018 Jul 20**. doi: 10.1097/j.pain.0000000000001350. PMID: 30036295. [Epub ahead of print]

The left dorsolateral prefrontal cortex (DLPFC) is involved in the experience and modulation of pain, and may be an important node linking pain and cognition. Repetitive transcranial magnetic stimulation (rTMS) to the left DLPFC can reduce chronic and experimental pain. However, whether left DLPFC rTMS can influence the development of chronic pain is unknown. Using repeated intramuscular injection of nerve growth factor (NGF) to induce the development of sustained muscle pain (lasting weeks), thirty healthy individuals were randomized to receive 5 consecutive daily treatments of active or sham left DLPFC rTMS, starting before the first NGF injection on day 0. Muscle soreness and pain severity were collected daily for 14 days and disability on every alternate day. Before the first and one day after the last rTMS session, anxiety, depression, affect, pain catastrophizing and cognitive performance on the attention network test were assessed. Left DLPFC rTMS treatment compared to sham was associated with reduced muscle soreness, pain intensity, and painful area ($p<0.05$), and a similar trend was observed for disability. These effects were most evident during the days rTMS was applied lasting up to three days following intervention. Depression, anxiety, pain catastrophizing, and affect were unchanged. There was a trend toward improved cognitive function with rTMS compared to sham ($p=0.057$). These data indicate that repeated left DLPFC rTMS reduces the pain severity in a model of prolonged muscle pain. The findings may have implications for the development of sustained pain in clinical populations.

## CHRONIC PAIN (Continued)

### Prevalence of Chronic Pain with or without Neuropathic Characteristics in France Using the Capture-Recapture Method: A Population-Based Study.

Chenaf C[1,2], Delorme J[1,2], Delage N[1,2], Ardid D[1,3,2], Eschalier A[1,3,2], Authier N[1,3,2].

Pain. **2018 Jul 19**. doi: 10.1097/j.pain.0000000000001347. PMID: 30028790. [Epub ahead of print]

Capture-recapture methods are increasingly used to determine the prevalence of numerous chronic conditions, but have never been used in the context of chronic pain (CP). This study sought to provide up-to-date estimates of the prevalence of people experiencing CP ± neuropathic characteristics in France using the capture-recapture method. In 2013-2015, three data sources were employed: the French prescription drug database (D-list), the national hospital discharge database (H-list), and the French pain center database (P-list). Patients aged ≥18years treated with analgesic drugs for ≥6 months (D-list) or with a diagnosis of CP ± neuropathic characteristics (H and P lists) were included. Two successive capture-recapture analyses were conducted, with log-linear regression for each analysis performed. A total of 63557 and 9852 distinct cases of CP and chronic neuropathic pain were captured, respectively. The estimated prevalence of CP and chronic neuropathic pain in the adults ranged from 27.2% (95%CI: 26.1-28.4) to 32.7% (26.0-43.3) and from 5.55% (2.89-19.0) to 7.30% (6.40-8.41), respectively. Most patients were female, median ages were 67 (55-80) and 63 (51-76) years for chronic and neuropathic pain, respectively. The analgesic drugs most frequently used in CP patients were paracetamol (62.1%), weak opioids (39.7%), and non-steroidal anti-inflammatory drugs (32.7%), while in neuropathic pain patients, anticonvulsants (45.3%), tricyclic antidepressants (18.1%), and serotonin-norepinephrine reuptake inhibitors (13.3%) were more frequently used. This first electronic health record-based study on chronic pain using the capture-recapture method revealed a high prevalence of chronic pain, with a significant proportion of neuropathic pain patients.

### Race and Gender Are Associated with Opioid Dose Reduction Among Patients on Chronic Opioid Therapy.

Buonora M[1], Perez HR[2], Heo M[3], Cunningham CO[2], Starrels JL[2].

Pain Med. **2018 Jul 18**. doi: 10.1093/pm/pny137. PMID: 30032197. [Epub ahead of print]

**Objective:** Among patients with chronic pain, risk of opioid use is elevated with high opioid dose or concurrent benzodiazepine use. This study examined whether these clinical factors, or sociodemographic factors of race and gender, are associated with opioid dose reduction.

**Design and Setting**: A retrospective cohort study of outpatients prescribed chronic opioid therapy between 2007 and 2012 within a large, academic health care system in Bronx, New York, using electronic medical record data. Included patients were prescribed a stable dose of chronic opioid therapy over a one-year "baseline period" and did not have cancer.

**Methods:** The primary outcome was opioid dose reduction (≥30% reduction from baseline) within two years. Multivariable logistic regression tested the associations of two clinical variables (baseline daily opioid dose and concurrent benzodiazepine prescription) and two sociodemographic variables (race/ethnicity and gender) with opioid dose reduction.

**Results:** Of 1,097 patients, 463 (42.2%) had opioid dose reduction. High opioid dose (≥100 morphine-milligram equivalents [MME]) was associated with lower odds of opioid dose reduction compared with an opioid dose <100 MME (adjusted odds ratio [AOR] = 0.69, 95% confidence interval [CI] = 0.54-0.89). Concurrent benzodiazepine prescription was not associated with opioid dose reduction. Black (vs white) race and female (vs male) gender were associated with greater odds of opioid dose reduction (AOR = 1.82, 95% CI = 1.22-2.70; and AOR = 1.43, 95% CI = 1.11-1.83, respectively).

**Conclusions:** Black race and female gender were associated with greater odds of opioid dose reduction, whereas clinical factors of high opioid dose and concurrent benzodiazepine prescription were not. Efforts to reduce opioid dose should target patients based on clinical factors and address potential biases in clinical decision-making.

## OTHER RESEARCH OF INTEREST

### Individual Research Results Should Be Shared With Participants More Often, Says New Report; Recommends Framework for Decision-Making

National Academies of Sciences, Engineering, and Medicine, **July 10, 2018**, Washington, D.C., News Release.

When conducting research involving the testing of human biospecimens, investigators and their institutions should routinely consider whether and how to return individual research results on a study-specific basis through an informed decision-making process, says a new report from the National Academies of Sciences, Engineering, and Medicine. Decisions on whether to return individual research results will vary depending on the characteristics of the research, the nature of the results, and the interests of participants.

The undertaking of biomedical research with human participants — from exploratory, basic science inquiries to clinical trials using well-validated tests — often includes development of laboratory test results associated with an individual research participant. Recent changes to federal regulations have promoted transparency and allowed individuals greater access to these results; however, regulations are not consistent, the report says. For example, the Centers for Medicare & Medicaid Services (CMS) prohibits the return of results from laboratories that are not certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), but in some circumstances the Health Insurance Portability and Accountability Act of 1996 (HIPAA) may require the return of results requested by a participant, regardless of whether they were generated in a CLIA-certified laboratory. CLIA requirements ensure the quality and integrity of data, accurate reconstruction of test validation and test performance, and the comparability of test results regardless of performance location.

“There is a long-standing tension in biomedical research arising from a conflict in core values — the desire to respect the interests of research participants by communicating results versus the responsibility to protect participants from uncertain, perhaps poorly validated information,” said Jeffrey Botkin, associate vice president for research and professor of pediatrics at University of Utah and chair of the study committee that wrote the report. “In weighing the complex and competing considerations, we recommend a transition away from firm rules embodied in current CLIA and HIPAA regulations toward a process-oriented approach favoring communication of results while seeking to enhance the quality of results emerging from research laboratories. Our hope is that this report will provide a road map toward better and more collaborative and transparent research practices that will benefit participants, investigators, and society more broadly.” [Link to full text of this NASEM News Release]

### Longitudinal resting state functional connectivity predicts clinical outcome in mild traumatic brain injury.

Madhavan R[1], Joel SE[2], Mullick R[3], Cogsil T[4], Niogi S[5], Tsiouris AJ[6], Mukherjee P[7], Masdeu JC[8], Marinelli L[9], Shetty T[10].

J Neurotrauma. **2018 Jul 19**. doi: 10.1089/neu.2018.5739. PMID: 30024343. [Epub ahead of print]

Mild traumatic brain injury (mTBI) affects about 42 million people worldwide. It is often associated with headache, cognitive deficits and balance difficulties but rarely shows any abnormalities on conventional CT or MR imaging. While in most mTBI patients the symptoms resolve within 3 months, 10-15% of patients continue to exhibit symptoms beyond a year. Also, it is known that there exists a vulnerable period post-injury, when a second injury may exacerbate clinical prognosis. Identifying this vulnerable period may be critical for patient outcome, but very little is known about the neural underpinnings of mTBI and its recovery. In this work, we used advanced functional neuroimaging to study longitudinal changes in functional organization of the brain during the 3-month recovery period post mTBI. Fractional amplitude of low frequency fluctuations (fALFF) measured from resting state functional MRI (rs-fMRI) was found to be associated with symptom severity score (SSS, r=-0.28, p=0.002). Decreased fALFF was observed in specific functional networks for patients with higher SSS, and fALFF returned to higher values when the patient recovered (lower SSS). In addition, functional connectivity of the same networks was found to be associated with concurrent SSS, and connectivity immediately after injury (<10 days) was capable of predicting SSS at a later time point (3 weeks to 3 months, $p<0.05$). Specific networks including motor, default-mode and visual networks were found to be associated with SSS ($p<0.001$), and connectivity between these networks predicted 3-month clinical outcome (motor and visual: $p<0.001$, default-mode: $p<0.006$). Our results suggest that functional connectivity in these networks are potential biomarkers for predicting mTBI recovery profiles and clinical outcome.

## OTHER RESEARCH OF INTEREST (Continued)

### The Association Between Military Sexual Trauma and Use of VA and Non-VA Health Care Services Among Female Veterans With Military Service in Iraq or Afghanistan.

Calhoun PS[1,2,3,4], Schry AR[1,2,3], Dennis PA[1,2,3], Wagner HR[1,2,3], Kimbrel NA[1,2,3], Bastian LA[5,6], Beckham JC[1,2,3], Kudler H[1,2,3], Straits-Tröster K[1,3,7].

J Interpers Violence. 2018 Aug;33(15):2439-2464. doi: 10.1177/0886260515625909. PMCID: PMC4956588. PMID: 26802046. Epub 2016 Jan 21.

Military sexual trauma (MST) has been linked with increased rates of mental health disorders among veterans. Few studies have addressed how MST is related to use of VA and non-VA health care. The purpose of the current study was to (a) examine the association between MST, combat experiences, and mental health outcomes (i.e., posttraumatic stress disorder [PTSD] and depression) and (b) examine the association of MST and use of VA and non-VA health care services among female veterans who served in Iraq and Afghanistan. Female respondents to a survey assessing Operation Enduring Freedom (OEF)/Operation Iraqi Freedom (OIF) veterans' needs and health (N = 185) completed measures of demographic variables, military history, combat exposure, MST, PTSD, and depression symptoms, and use of VA and non-VA health care. Overall, 70% of the sample experienced one or more combat-related experiences and 15.7% endorsed MST during deployment to Iraq or Afghanistan. MST and combat exposure were both positively associated with PTSD and depression symptoms even after controlling for the effects of demographic and military history variables. MST was associated with increased use of VA mental health services in bivariate results but was not independently related to VA service utilization after accounting for PTSD and depression symptoms. Approximately half of the women who reported MST had not used VA health care. Continued outreach and education initiatives may be needed to ensure veterans understand the resources available to address MST-related mental and physical health problems through the VA.

### Assessing Synaptic Density in Alzheimer Disease With Synaptic Vesicle Glycoprotein 2A Positron Emission Tomographic Imaging.

Chen MK[1], Mecca AP[2], Naganawa M[1], Finnema SJ[1], Toyonaga T[1], Lin SF[1], Najafzadeh S[1], Ropchan J[1], Lu Y[1], McDonald JW[2], Michalak HR[2], Nabulsi NB[1], Arnsten AFT[2], Huang Y[1], Carson RE[1], van Dyck CH[2].

JAMA Neurol. **2018 Jul 16**. doi: 10.1001/jamaneurol.2018.1836. PMID: 30014145. [Epub ahead of print]

**Importance:** Synaptic loss is well established as the major structural correlate of cognitive impairment in Alzheimer disease (AD). The ability to measure synaptic density in vivo could accelerate the development of disease-modifying treatments for AD. Synaptic vesicle glycoprotein 2A is an essential vesicle membrane protein expressed in virtually all synapses and could serve as a suitable target for synaptic density.

**Objective:** To compare hippocampal synaptic vesicle glycoprotein 2A (SV2A) binding in participants with AD and cognitively normal participants using positron emission tomographic (PET) imaging.

**Design, Setting, and Participants:** This cross-sectional study recruited 10 participants with AD and 11 participants who were cognitively normal between November 2015 and June 2017. We hypothesized a reduction in hippocampal SV2A binding in AD, based on the early degeneration of entorhinal cortical cell projections to the hippocampus (via the perforant path) and hippocampal SV2A reductions that had been observed in postmortem studies. Participants underwent high-resolution PET scanning with ((R)-1-((3-(11C-methyl-11C)pyridin-4-yl)methyl)-4-(3,4,5-trifluorophenyl)pyrrolidin-2-one), a compound more commonly known as 11C-UCB-J, for SV2A. They also underwent high-resolution PET scanning with carbon 11-labeled Pittsburgh Compound B (11C-PiB) for β-amyloid, magnetic resonance imaging, and cognitive and neurologic evaluation.

**Main Outcomes and Measures**: Outcomes were 11C-UCB-J-specific binding (binding potential [BPND]) via PET imaging in brain regions of interest in participants with AD and participants who were cognitively normal.

**Results:** Ten participants with AD (5 male and 5 female; mean [SD] age, 72.7 [6.3] years; 10 [100%] β-amyloid positive) were compared with 11 participants who were cognitively normal (5 male and 6 female; mean [SD] age, 72.9 [8.7] years; 11 [100%] β-amyloid negative). Participants with AD spanned the disease stages from amnestic mild cognitive impairment (n = 5) to mild dementia (n = 5). Participants with AD had significant reduction in hippocampal SV2A specific binding (41%) compared with cognitively normal participants, as assessed by 11C-UCB-J-PET BPND (cognitively normal participants: mean [SD] BPND, 1.47 [0.37]; participants with AD: 0.87 [0.50]; P = .005). These reductions remained significant after correction for atrophy (ie, partial volume correction; participants who were cognitively normal: mean [SD], 2.71 [0.46]; participants with AD: 2.15 [0.55]; P = .02). Hippocampal SV2A-specific binding BPND was correlated with a composite episodic memory score in the overall sample (R = 0.56; P = .01).

**Conclusions and Relevance:** To our knowledge, this is the first study to investigate synaptic density in vivo in AD using 11C-UCB-J-PET imaging. This approach may provide a direct measure of synaptic density, and it therefore holds promise as an in vivo biomarker for AD and as an outcome measure for trials of disease-modifying therapies, particularly those targeted at the preservation and restoration of synapses.

###